[illegible]

BRAIN

A JOURNAL OF NEUROLOGY

MACMILLAN AND CO., LIMITED
LONDON - BOMBAY - CALCUTTA
MELBOURNE

THE MACMILLAN COMPANY
NEW YORK - BOSTON - CHICAGO
ATLANTA - SAN FRANCISCO

THE MACMILLAN CO. OF CANADA, LTD
TORONTO

46

Brain

A Journal of Neurology

EDITOR
GORDON HOLMES, M.D.

ASSISTANT EDITORS
J. G. GREENFIELD, M.D. AND F. M. R. WALSHE, M.D.

WITH THE HELP OF

IR BYROM BRAMWELL, M.D.
IR FARQUHAR BUZZARD, M.D.
IR HENRY HEAD, M.D., F.R.S.
PERCY SMITH, M.D.

SIR CHARLES SHERRINGTON,
M.D., F.R.S.
SIR J. PURVES-STEWART, M.D.
JAMES TAYLOR, M.D

VOLUME LII

MACMILLAN AND CO., LIMITED
ST. MARTIN'S STREET, LONDON
NEW YORK: THE MACMILLAN COMPANY
1929

916268

CONTENTS.

PAGE

Hepatico-Lenticular Degeneration: A Final Note. Stanley Barnes and E. Weston Hurst 1

A Form of Myasthenia Gravis with Changes in the Central Nervous System. Douglas McAlpine 6

Arteriosclerotic Parkinsonism. Macdonald Critchley 23

A Case of the Progressive Hypertrophic Polyneuritis of Dejerine and Sottas, with Pathological Examination. R. S. de Bruyn and Ruby O. Stern 84

A Case of Relapsing Interstitial Hypertrophic Polyneuritis. Wilfred Harris and Wilfrid D. Newcomb 108

A Clinical Study of Twenty-one Cases of Tumour of the Hypophyseal Stalk. J. W. Beckmann and L. S. Kubie 127

The Pathology of Measles Encephalomyelitis. J. Godwin Greenfield ... 171

The Bi-Coloured Guaiac Test. Dr. Eugene de Thurzo 196

A Clinical Study of an Heredo-Familial Disease resembling Disseminated Sclerosis. Fergus R. Ferguson and Macdonald Critchley ... 203

Tumours of the Pineal, Corpora Quadrigemina and Third Ventricle, the Inter-Relationship of their Syndromes and their Surgical Treatment. Mark Albert Glaser 226

Subacute Combined Degeneration of the Cord: Symptomatology and Effects of Liver Therapy. C. C. Ungley and M. M. Suzman ... 271

A Study of the Histopathology of Tabes Dorsalis with Special Reference to Richter's Theory of its Pathogenesis. Ruby O. Stern... ... 295

Diplopia without Extra-Ocular Palsies, caused by Heteronymous Defects in the Visual Fields associated with Defective Macular Vision. L. S. Kubie and J. W. Beckmann 317

Studies on the Optic Thalamus of the Insectivora.—The Anterior Nuclei. W. E. Le Gros Clark 334

The Significance of Some Variations in the Knee-Jerk in Diseases of the Central Nervous System. E. A. Blake Pritchard 359

A Study of a Case of Cervical Glioma. James K. Slater and F. E. Reynolds 425

PAGE

A Study of the Pathology of a Case of Glioma Cerebri. F. E. Reynolds 436

The Corpus Callosum and its Tumours. Redvers Ironside and Manfred Guttmacher 442

Skin Reactions in a Case of Cervical Sympathetic Paralysis, with a Note on their Practical Application to Neurology. Kenneth E. Harris .. 484

The Respiratory Rhythm in its Relation to the Mechanism of Thought. F. L. Golla and S. Antonovitch 491

Electromyographic Studies of Voluntary Movements in Paralysis Agitans. E. A. Blake Pritchard 510

Proceedings of the Section of Neurology of the Royal Society of Medicine, November 14 530

Notices of Recent Publications 117, 262, 547

Index to Vol. LII 553

LIBRARY

APRIL, 1929.

BRAIN.

PART 1, VOL. 52.

HEPATO-LENTICULAR DEGENERATION; A FINAL NOTE.

BY STANLEY BARNES AND E. WESTON HURST.

IN a former communication to this Journal [1] we described a group of four cases, three of which had been demonstrated at the Neurological Section of the Royal Society of Medicine in January, 1924 [2]. A further note in this Journal [3] recorded the final results after the death of the third patient; this communication completes the record of the fourth patient (Daniel B.), who died at the age of 11 in the General Hospital, Birmingham, on August 19, 1928.

Daniel B. was first examined in 1923, when he was 6 years of age, attention having been directed to the family by reason of a brother and sister both having shown signs of lenticular degeneration. At that date, it was found that he had an enlarged and hard liver, but that he was in no way inconvenienced by his abnormality, and no evidence of nervous disease could be obtained.

At the age of 7½, he had a severe attack of diarrhœa and vomiting, associated with fever of moderate degree, and lasting for several days. He probably became lightly jaundiced in this attack, but no observation by a reliable observer is available on this point. He made a complete clinical recovery from this attack, and remained in fair but impaired health for the next three years. The impairment in health was of a general character; he did not grow so rapidly as he should, nutrition was poor and lassitude of an unusual degree for a boy of his age was a predominant characteristic. For much of this period he was kept away from school, and this doubtless accentuated his mental backwardness. Nevertheless, those suggestions of choreic or athetoid movements of limbs and face which had been noted previously (see *Brain*, 1926, vol. xlviii, pp. 309-311) never advanced to such a degree that they could be recognized as beyond the limits of the normal; they appeared to express a personal eccentricity rather than evidence of organic disease.

In June, 1928, his abdomen began to swell, and he was again admitted to hospital on July 9, remaining there until his death on August 19, 1928.

On readmission (aged 11), he was poorly nourished, had a sallow complexion, but no jaundice. The abdomen was tightly distended with free fluid, and respiration was somewhat embarrassed. He lay placidly in bed, took an intelligent interest in his examination, and answered questions correctly if somewhat slowly. No spontaneous movements were present, and on voluntary movement no chorea or athetosis was observed.

No pigmentation of the Kayser-Fleischer type was to be found on careful examination with a lens, but the slit lamp was not used on this occasion.

On July 17 he was tapped, and 190 oz. of clear straw-coloured fluid removed. Even after this was done, neither liver nor spleen could be palpated during deep inspiration. On July 21, the abdomen was beginning to fill up again, and slight jaundice was noted; a second paracentesis (210 oz.) became necessary on July 30, and thereafter he had some pain and tenderness over the liver region. Further tapping of the abdomen became necessary on August 14 (300 oz.), and it was noted that he was getting much weaker, more listless and drowsy.

During the night of August 16-17, he became mildly delirious and complained of abdominal pain, and on the morning of the 17th was semi-conscious and had incontinence of urine. Throughout the day at intervals of ten to fifteen minutes he suffered from tetanic spasms affecting chiefly the upper part of his body. "He would give a sudden cry, almost like a meningitic cry, and his mouth would be drawn up resembling a risus sardonicus, with some degree of head retraction. The arms, and to some extent the legs, would perform definite athetoid movements." (Note by the house physician). Between the attacks he lay in a semi-flexed attitude, relaxed, and on his side, speech being unintelligible except for occasional utterances.

The attacks continued, and as he appeared to be *in extremis* and in great distress, opium was given; the restlessness and tetanic attacks subsided for several hours, but at 2 a.m. on August 18 he again became restless, gave a sudden loud cry, and died almost immediately.

Throughout the period of six weeks during which he was in the hospital, the temperature never remained normal. There was as a rule a variation of one and a half degrees between his morning (lower) and evening temperatures. The highest recorded was on July 15, when it reached 101·2° F., whilst on several occasions it was as low as 97° F. It was an irregular hectic temperature of moderate degree, and during the last twenty-four hours varied between 100° F. and 98° F. No clinical cause, other than such as might be attributed to his liver disease, could be discovered for his fever.

The post-mortem examination was made six hours after death. The following are the notes made by Dr. F. W. M. Lamb, Assistant Pathologist, General Hospital, Birmingham:—

The body is that of an emaciated boy, aged 11.

The abdomen was distended with fluid of greenish-yellow colour, containing flakes of fibrin, but otherwise translucent and somewhat gelatinous. About three pints altogether were taken from the abdomen. Each pleura contained rather less than a pint of clear yellow fluid.

The skin showed a general sallow tint, probably icteric.

The conjunctivæ also showed a slight but general icteric tint.

The heart weighed about 200 grm., and showed no gross abnormality except for some pallor of the muscle, and yellow staining of the endocardium. The epicardium showed several petechial hæmorrhages.

Lungs: Slightly œdematous with yellow fluid (jaundice). Terminal hypostatic pneumonia.

Liver: 650 grm. Small, extremely atrophic and fibrotic. Areas of yellow (bile-stained) hyperplastic liver tissue separated from each other by strands of dense white fibrous tissue. Typical so-called "multilobular" cirrhosis.

Kidneys: 270 grm. No gross abnormality.

Spleen: 330 grm. large. Marked congestion of some duration, probably result of portal congestion.

Stomach, small and large intestines: No gross abnormality.

Pancreas: Appeared firmer than usual, but showed no trace of fibrosis.

Lymph glands at pylorus, along aorta, round pancreas, and in superior mediastinum, distinctly enlarged and congested.

Brain: Removed and preserved in 10 per cent. formol-saline, not cut except horizontally through outer part of hemispheres to allow penetration of formalin.

MICROSCOPICAL EXAMINATION. (E. W. H.)

The liver.—The appearances vary in different parts of the organ.

In many regions the liver is intersected by numerous bands of fibrous tissue attaining often a diameter of 2 mm. and subdividing the parenchyma into areas of comparatively large size (5 mm. diameter); in some instances partial subdivision of these large areas by much finer tracts of fibrous tissue occurs. Although in a few places near the edge of a lobule small groups of liver cells lie isolated by strands of connective tissue, on the whole the demarcation between the two is fairly sharp. The fibrous tissue shows a moderate number of small blood-vessels and new-formed bile-ducts; it is however not particularly rich in either. Areas infiltrated with round cells; occasional plasma cells and rare eosinophil leucocytes, occur.

In other regions the amount of fibrous tissue is greatly in excess of that of the parenchyma, which is represented by small masses rarely exceeding 1 mm. in diameter. Here the line of demarcation between liver and connective tissue is less definite and the liver cells are frequently split up into small groups by new-formed tissue. The formation at the periphery of the masses of numerous young bile-ducts of a less fully developed type than found elsewhere, the more intense round-cell infiltration and the scanty deposition of very delicate collagen fibrils, indicate that in such areas the destruction of liver tissue was actively progressing at or shortly before death.

Fatty degeneration of the liver cells is conspicuous in certain areas and plugs of bile-stained material can be seen in the fine bile capillaries or in the protoplasm of the secreting cells.

The nervous system.—Macroscopically no abnormality was detected.

The brain was subjected to an examination similar to that already recorded in our previous communications.

In the cortex the nerve cells were frequently slightly swollen with granular staining of the protoplasm and tiny vacuoles or a fine meshwork at the periphery. Such appearances were diffusely distributed and in no way confined to one area or cell-group of the nervous system; they were of the nature of acute changes ascribable to a terminal toxic state. Very occasionally a vessel in the subcortical white matter showed scanty perivascular infiltration with lymphocytes; not only was this occurrence rare, but it was never sufficiently marked to attract attention except on the closest examination. The glial cells were not obviously affected: no glial increase was evident and the peculiar Alzheimer cells seen in our previous cases were not present.

The lenticular nucleus, caudate nucleus and basal ganglia generally showed no definite pathological changes.

The brain-stem and cerebellum were normal.

The spinal cord was not examined.

The eyes.—Many sections were examined from both corneæ (the identity of which was unfortunately lost). One showed no pigmentation of any kind. The other contained a very few fine pigment granules situated not in Descemet's membrane but in some of the epithelial cells of the posterior surface. Over large stretches of this cornea the epithelium was devoid of granules, but occasionally groups of cells were seen containing tiny dark brown grains to the number of from one to six or eight in each cell. The staining reactions and solubilities of the pigment were those given by Hall as typical of the corneal deposits in hepato-lenticular degeneration, and not those of the pigment in our last case, which, it will be remembered, though confined to Descemet's membrane, differed from the usual in several particulars. It is difficult to decide whether this pigment, scanty in amount and atypical in situation, is on account of its reactions to be classed with the corneal pigment of other cases; it does not appear to be a formol precipitate.

One of the most remarkable features of this case (No. 4 of our series) is that in the final phase he should have exhibited a series of tetanoid attacks similar to those which were such a feature in the same stage of Case 1, although in the latter case clear clinical evidence of lenticular disease was present, whilst none could be obtained clinically or post-mortem in Case 4. Such a type of convulsion has not been observed by us before in cases of other forms of cirrhosis of the liver, when the moribund period is usually characterized by coma rather than convulsions, and when, if convulsions occur, they are of the epileptic type. It will be noted that in neither Case 1 nor Case 4 were the convulsions of the usual epileptic type, neither being accompanied by unconsciousness. The "fits" resembled the spasms of tetanus more than the crises of epilepsy, and were accompanied by evidence of fear, anxiety, sweating and severe pain. During the spasms an irregular form of decerebrate rigidity was developed, the precise form not being identical in the two cases.

It is difficult to give any adequate reason for the development of these spasms, especially as in the first case obvious gross changes were present in the putamen and cortex, whilst in the last one cortical changes of a very light type only were found. The suggestion, however, is put forward that :

(1) The patients both died during an attack of severe toxæmia.

(2) That during this period a large amount of toxin, untrapped by the damaged liver, flooded the nervous system.

(3) Widespread poisoning (and sudden temporary suspensions of function) occurred in various nuclear groups of the nervous system.

(4) The groups chiefly so affected were those which would ultimately have degenerated if the patient had not been previously killed by the severity of the liver disease, viz., the lenticular nucleus, and to a less degree the "middle level" cortex.

(5) The spasms would then be due to the unopposed activity of the "lowest level" innervation, the controlling effects of the lenticular nucleus and the "middle level" cortex having been temporarily abolished by the toxæmia, which left the "upper level" cortex substantially unaffected, whilst

(6) Death ensued when the "lowest level" and medullary group also ceased to function, partly owing to exhaustion from spasms, partly because the poisoning effect (toxæmia) had spread to these nuclei.

REFERENCES.

[1] BARNES and HURST. *Brain*, 1925, **48**, 279.
[2] BARNES. *Proc. Roy. Soc. Med.*, Neurol. Sect., 1924, **17**, 34.
[3] BARNES and HURST. *Brain*, 1926, **49**, 36.

A FORM OF MYASTHENIA GRAVIS WITH CHANGES IN THE CENTRAL NERVOUS SYSTEM.

BY DOUGLAS McALPINE, M.D.

(From the Pathological Laboratory of the Hospital for Epilepsy and Paralysis, Maida Vale, London.)

		PAGE
1.	Clinical Account of the Case ..	6
2.	Pathological Findings ..	9
3.	Significance of Mucocytic Degeneration	12
4.	Myasthenia Gravis as a Possible Sequel to Epidemic Encephalitis ..	15
5.	Discussion ..	20
6.	Summary ..	21
7.	Literature ..	22

This paper is based on a clinical and pathological account of a case of myasthenia gravis. Certain morbid changes were found in the central nervous system which have not previously been described.

Clinical Account of the Case.

G. E. H., a probationer nurse, aged 22, was admitted to the Hospital for Epilepsy and Paralysis, Maida Vale, London, on February 15, 1924, under the care of Dr. H. Campbell Thomson, who subsequently handed the case over into my care with a diagnosis of myasthenia gravis.

History.—The patient had enjoyed good health until October, 1923, when she noticed a slight difficulty in articulating certain words. A month later the lower limbs became weak after standing for any length of time. In December the arms were similarly affected. During the first week in January, 1924, she saw double for the first time. The patient particularly noticed that all her symptoms were more marked towards the evening, or after much exertion. In January she developed a right otitis media which was followed by an intermittent discharge from the ear. No history of insomnia, somnolence, pain or involuntary movements could be elicited. As far as the patient was aware she had had no rise of temperature, except possibly when the ear first discharged. There was nothing of importance in the family or personal histories.

Condition on February 18, 1924.—The patient appeared to be a healthy young woman, though inclined to stoutness. She was intelligent and able to give a clear account of her illness. The pupils were equal and reacted well to light and accommodation. There was a slight but definite impairment of ocular movements in a lateral direction. Diplopia could be easily induced by asking the patient to perform repeated lateral movements of the eyes. Upward movement of the eyeballs was slightly restricted. Moderate bilateral ptosis was present, which varied in degree from day to day, but which was always more marked towards the evening. The facial muscles were bilaterally weak, more especially the orbicularis oculi. The circumoral muscles were less affected but the degree of paresis was sufficient to prevent the act of whistling, which had been possible before her illness. The masseters and temporal muscles contracted well and were not atrophied. The voice was considerably altered; it was feeble in tone and somewhat monotonous; at times dysarthria was marked, rendering her speech difficult of comprehension. The palate moved well on phonation but was easily fatigued. The tongue was protruded well and showed no atrophy or tremor; the patient had difficulty, however, in keeping it protruded for any length of time. The sterno-mastoid muscles and upper portion of the trapezii were not atrophied or weak, but both they and the extensor and flexor muscles of the neck tired easily.

Upper limbs.—Muscular atrophy was absent. Motor power was quite good, but repeated movements, especially at the shoulder, were quickly accompanied by lessened force and a subjective sensation of fatigue. The reflexes were brisk and equal on the two sides. There was no sensory loss.

Trunk.—No paresis of the abdominal or intercostal musculature could be detected. The abdominal reflexes were brisk and equal on the two sides.

Lower limbs.—Motor power was relatively good. The knee-jerks and ankle-jerks were brisk. In the case of the knee-jerk, taps on the patellar tendon repeated at short intervals resulted in a definite decrease in the degree of extension. Both plantar responses were flexor in type. There was no sensory loss. Gait was normal.

Electrical reactions.—A fairly typical myasthenic reaction was obtained in the fore-arm muscles.

Sphincters.—Control over these was normal.

Heart.—This was not enlarged and the heart sounds were normal.

Abdomen.—The liver and spleen were not enlarged.

Urine.—This was free from albumin and sugar.

Endocrine glands.—The thyroid gland did not appear enlarged. No definite enlargement of the thymus gland could be made out either by percussion or on X-ray examination. Menstruation was normal. There was no pigmentation of the skin and the blood-pressure figures were: Systolic 125, diastolic 75.

Ear, nose and throat.—There was a right otitis media, with a purulent discharge from this ear. The tonsils were enlarged and appeared septic.

Serological findings.—The blood Wassermann reaction was negative. The cerebro-spinal fluid was clear and was not under tension. The Wassermann reaction was negative. There were 3-5 cells per c.mm. and 0·035 per cent. of protein. The Lange gold curve was normal.

Progress.—Treatment of the otitis media was unsatisfactory, and on this account it was decided to remove the tonsils. These were dissected out on July 19. During many months in hospital her condition slowly grew worse. The muscular weakness in her limbs and elsewhere, which at first was only apparent after exertion, became permanent. The neck muscles, towards the end of her life, were considerably affected, so that at times, especially towards the evening, she was forced to support her chin with her hands. Dysarthria became permanent and latterly her speech was nearly incomprehensible. Dysphagia appeared about four months before death, and to this was added difficulty in mastication. Diplopia with partial external ophthalmoplegia were constantly present. The most distressing symptom, however, was dyspnœa, which was first noted in November, 1924. This occurred in attacks and was sometimes brought on by crying, which seemingly fatigued the diaphragm and intercostal muscles. The attacks lasted sometimes as long as four hours. The reflexes remained unaltered throughout the illness. On the morning of January 21, 1925, she had a severe attack of dyspnœa which persisted throughout the day with full retention of consciousness. Respiration was exceedingly shallow and difficult. Towards the evening she became comatose and died a few hours later.

Clinical summary.—A female, aged 23, developed dysarthria in October, 1923, followed a month later by diplopia. She readily became fatigued. These symptoms were always more marked towards the evening or after exertion. There was no history of sleep disturbance, pains or involuntary movements. When examined in February, 1924, she showed the following signs: A moderate bilateral and variable ptosis, diplopia and marked weakness of the orbicularis oculi and to a less extent of the lower facial musculature. Fatigue was easily induced in the soft palate, tongue and limbs. The reflexes and sensation were normal. During many months in hospital her condition gradually grew worse; her symptoms were always worse towards the end of the day. Dysphagia, weakness of the neck muscles and permanent paresis of the limbs with attacks of dyspnœa became marked, and she died in a respiratory attack in January, 1925, her illness having lasted fifteen months.

PATHOLOGICAL FINDINGS.

At the post-mortem examination, performed seven hours after death, no abnormality of the brain or spinal cord was noted. The thymus gland was much enlarged and weighed in the fresh state 48·5 grm. Parts of the following organs were removed for histological examination: thymus and thyroid glands, liver, spleen, kidney, suprarenal gland, uterus, Fallopian tube, ovary and heart. Portions of certain muscles were also removed, e.g., tongue, clavicular head of left sterno-mastoid, right external rectus, diaphragm, upper part of right trapezius, right biceps and deltoid.

Histological examination.—The various internal organs appeared normal with the exception of the thymus. The general structure of the gland was normal, but there was considerable increase in the depth of the cortex. The medulla contained about a normal proportion of Hassall's corpuscles. Owing to the kindness of Professor J. McIntosh, I was able to compare the sections with those from a young woman, aged 20, who suddenly died whilst dancing and in whom the only post-mortem finding of importance was an enlarged thymus gland. The histological appearances in the two cases were practically identical and pointed to a simple hypertrophy.

Numerous sections of the muscles mentioned above were carefully examined with completely negative results. No collection of cells resembling lymphorrhages were seen.

Nervous system.—The brain and spinal cord were fixed in a 10 per cent. solution of formalin. Various parts of the cortex, the basal ganglia and cerebellum were examined.

The brain-stem from the subthalamic region downwards was cut in serial section. Many sections of the spinal cord at various levels were studied. The methods used were; hæmatoxylin and van Gieson, hæmatoxylin and eosin, Nissl, Weigert-Pal, Loyez, Anderson's neuroglial stain, Scharlach R., Bielschowsky and Mayer's mucicarmine.

Cortex.—Sections from the frontal, rolandic, parietal and occipital regions were examined. The cells of the various layers appeared normal. The vessels were normal except for deposits of mucin in the perivascular spaces. The Weigert-Pal preparations showed normal staining of the fibres, except when they were interrupted by mucocytes, which had pushed the fibres aside, leaving clear rounded spaces of varying size. The meninges were normal except for infiltration with mucoid material; this will be referred to later.

Basal ganglia.—The cells of the various nuclei appeared plentiful and the great majority were normal. There was no evidence of perivascular lymphocytosis. The fibres of the internal capsule stained well but were interrupted at frequent intervals by mucocytes of varying size.

Subthalamic region.—The various nuclei, such as the corpus Luysii, red nucleus, substantia nigra, tuber cinereum, and the nuclei in the neighbourhood of the third ventricle were normal, and no changes were seen in the vessels or neuroglial cells.

Brain-stem.—The nuclei of the cranial nerves were normal with the exception of the third nerve nucleus, a few cells of which showed some variation in their staining qualities but no definite evidence of chromatolysis. No intracellular lipoid material was seen. The vessels and meninges throughout the brain-stem were free from any cellular infiltration, except at the junction of the medulla and pons, where a small vessel showed a discrete perivascular lymphocytosis. Mucoid degeneration was present throughout the white matter of the brain-stem.

Spinal cord.—As the changes about to be described were similar in all parts of the cord, the following description of those present in the cervical region is applicable to other parts of the cord. The anterior horn cells were normal. The vessels showed well-marked perivascular infiltration with round cells. This was a striking feature in the majority of the sections examined, four to six rings of cells being commonly seen. The cells were sometimes arranged in the form of a cuff, similar to that seen in epidemic encephalitis. The majority of the cells were lymphocytes of medium size; their nuclei, containing a number of chromatin dots, stained well with hæmatoxylin. The nuclei varied in shape, some being rounded, others oval. Other cells present were small lymphocytes with a more deeply-staining nucleus, and hyaline endothelial cells with a large oval nucleus. Plasma cells were scarce. The perivascular infiltration was most marked near the postero-median fissure and in the region of the posterior root entry zone. In one or two sections cuffing was seen around a vessel in the anterior horn.

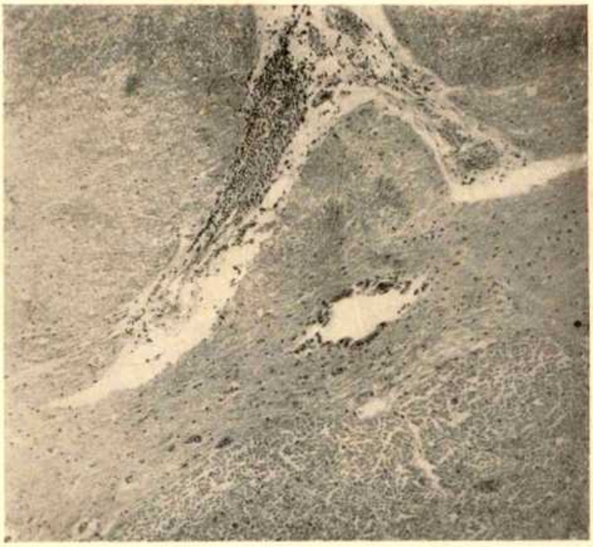


FIG. 1.—Section through mid-dorsal region of the cord, showing perivascular infiltration around a vessel in the antero-median fissure. Hæmatoxylin and eosin. x 60.

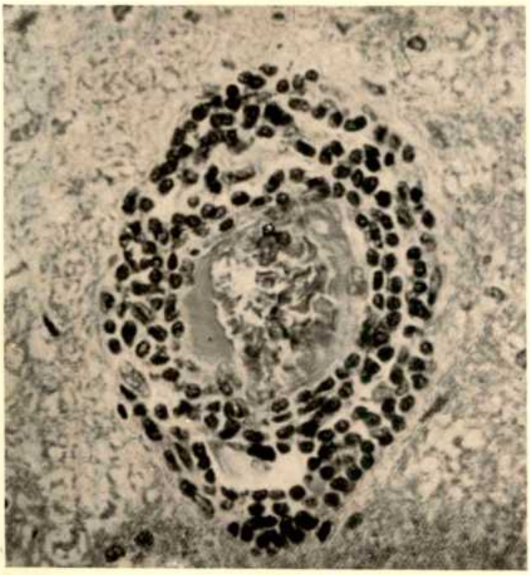


FIG. 2.—A section from the cervical enlargement, showing details of the perivascular infiltration. Hæmatoxylin and eosin. x 480.

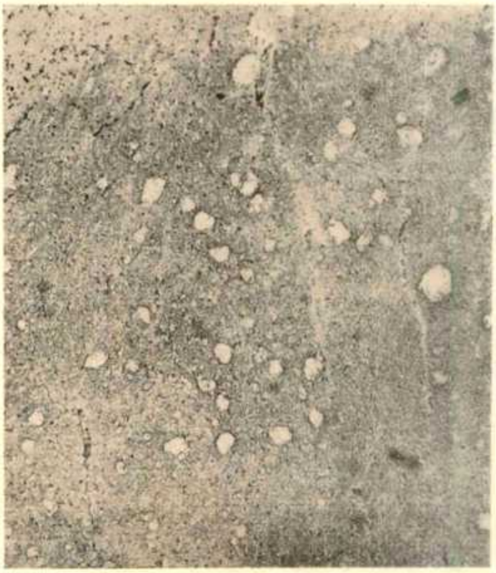


FIG. 3.—Numerous mucocytes in the white matter of the spinal cord. Hæmatoxylin and van Gieson. x 50.

To illustrate Dr. Douglas McAlpine's paper.

Recent hæmorrhages into the grey matter of the anterior horns were observed in several sections, being absent from the brain-stem and brain itself. There was a slight but definite increase of neuroglial cells, chiefly around the anterior horns and posterior root entry zone. The meninges were normal except for deposits of mucoid material beneath them. In celloidin sections small and large mucocytes were numerous throughout the length of the cord.

Weigert-Pal sections showed no tract degenerations and were normal, except for a riddled appearance due to the mucocytes.

Mucoid Degeneration.

As deposits of mucin were extremely numerous, their character and disposition will be considered in more detail. In sections stained by the method of Nissl, especially when thionin blue was used, rounded or irregularly-shaped areas staining a faint pink colour were seen in the white matter. These areas were stained a bright blue colour with hæmatoxylin. The appearances in Weigert-Pal sections have already been described. The nature of this degeneration was made clear by staining sections with Mayer's mucicarmine, which gave a bright pink colour to the areas. This stain has been described as specific for mucin.

In a section through the cortex and adjacent subcortical white matter, the process was observed to be intense in the white matter. The vessels of the cortex itself were in many places surrounded by mucin. A diffuse infiltration of the meninges was observed in many places, and the process tended to invade the adjacent cortex. The general appearance of the degeneration in this region suggested that mucin was transported to the surface of the brain from the subcortical white matter through the agency of the perivascular lymphatics. The nuclei of the basal ganglia were relatively free, but vessels here and there contained mucin in their perivascular spaces. The internal capsule showed a great quantity of mucin scattered about in areas of varying size. Throughout the brain-stem the process was generalized, affecting chiefly the white matter. The degeneration in most places was at an early stage, the areas being comparatively small in size. The process extended up to the meninges and under the ependyma. The cortex of the cerebellum was unaffected, but in its white matter and the dentate nucleus the process was more marked than in the brain-stem or basal ganglia. In the spinal cord the degeneration was particularly intense. It was practically confined to the white matter

The areas varied considerably in size, some being quite large, due to fusion of several adjacent mucocytes. The mucoid material also tended to collect along the entering posterior root fibres.

Summary of Histological Findings.

The various visceral and endocrine organs were normal, with the exception of the thymus gland which was markedly hypertrophied. No lymphorrhages were observed in the muscles examined. The cerebral cortex, subcortical white matter and basal ganglia were normal apart from extensive mucocytic degeneration, which especially involved the white matter. The various motor nuclei in the brain-stem were unaltered except that a few of the cells of each third nucleus showed slight changes. The vessels were normal. Mucocytic degeneration was present. Many of the vessels of the spinal cord were markedly infiltrated with round cells. There was a slight degree of gliosis, especially around the anterior horns. The motor cells were normal at all levels. Mucocytes were more numerous in the cord than elsewhere. The meninges were normal.

THE SIGNIFICANCE OF MUCOCYTIC DEGENERATION.

Reference has been made to areas of mucoid degeneration. A review of the literature shows that this morbid change has attracted but little attention until quite recently. Buscaino [6], in studying brains from some cases of dementia præcox, found "grape-like areas" of disintegration in the white matter. He considered that these were the result of a true process of disintegration due to a lesion of the nerve fibres and neuroglial cells. Subsequently other workers on this subject found these "grape-like bodies" in a variety of pathological and even normal brains. It was shown that this form of degeneration was not apparent in frozen sections but only in those previously treated with alcohol or nitric alcohol. On this account Salustri [21], Ansalone [1], S. d'Antona [2] and others considered that they were artefacts. Lhermitte and Radovici [14], in cases of epidemic encephalitis, observed rounded areas with clear-cut edges, which stained red by the method of Casamajor, and violet-red by the method of Bonfiglio. The process was most marked in the white matter of the brain and spinal cord. It was sometimes observed in neuroglial cells, but more often it was extracellular and closely connected to the myelin sheaths. Grynfeltt [11], using Mayer's mucicarmine, was the first to recognize the nature of the degeneration and its origin in the interfascicular glial cells. He introduced the word "mucocyte" to indicate the cellular origin and chemical nature of this form of degeneration. His work was based on the examination of a brain of an old man, but he gave no details as to the nature of the disease from which the man suffered. Lhermitte, Kraus and Bertillon [15] described fully the staining reactions of these "mucin-like bodies," which they observed in a case of post-encephalitic Parkinsonism, but denied their cellular origin.

Greenfield [9] observed the formation of mucin or mucinoid droplets in the bodies of interfascicular glial cells in epidemic encephalitis. He considered that the change may take place early, as he had observed it on the twenty-fourth day of the disease. Pélissier [20] studied this process in great detail in a case of chronic encephalitis. He described the distribution of mucocytes in the white matter throughout the brain, and stated that their presence in the grey matter can be explained by a migration of the mucocytes from the white matter. He also found mucoid material under the ependyma. He described in detail the formation of mucocytes from interfascicular glial cells.

Bailey and Schaltenbrand [3] observed this type of degeneration in a case of Schilder's disease. They adopted the term "mucocyte" as used by Grynfeltt and Pélissier, and proved that the interfascicular cells referred to by these authors are oligodendroglial cells. Grynfeltt and Pélissier showed that the mucin, formed for the most part in the white matter, found its way towards the surface of the brain on the one hand, and towards the ventricular cavities on the other. This migration appeared to be carried out through the agency of the perivascular lymphatic spaces.

Pagès, Bénoit and Pèlissier [18] have deduced from these findings the possibility of mucin appearing in the cerebro-spinal fluid in certain diseases. The method which they used for the detection of this substance in the fluid is that of Derrien, the details of which are described in their paper. They have searched for mucin in 130 cases. In fifteen cases in which the fluid was withdrawn during spinal anæsthesia for various operations, no mucin was found. It was present, however, in a variety of organic neurological conditions, such as cerebral arteriosclerosis, epilepsy, dementia præcox and uræmia. It occurred most frequently in cases of chronic epidemic encephalitis.

Ferraro [8], in a recent critical review of the subject, based on his own work and that of others, came to the following conclusions:—

(1) The "grape-like body" of Buscaino and the mucocyte of Grynfeltt and Pélissier are identical.

(2) Their absence from frozen sections does not necessarily imply an

artefact, since the action of alcohol may reveal a form of lesion otherwise not apparent.

(3) The relationship between acute swelling of the oligodendroglia and the formation of mucocytes has not, in his opinion, been satisfactorily demonstrated. The absence of striking changes in the nuclei in the area of degeneration is a point against the origin of mucocytes from degenerated neuroglial cells.

I have attempted to repeat certain of Ferraro's experiments, but without any convincing results. The following are my conclusions, tentatively given: (1) Small rounded areas of mucin are present in frozen as well as celloidin sections of a large number of pathological conditions. No controls with normal material have been made. (2) In formalin-fixed material, which has been passed through celloidin, numerous irregularly-shaped areas corresponding to the large mucocytes of Grynfeltt and Pélissier have been found in the case of myasthenia gravis described in the present paper and in two cases of chronic epidemic encephalitis. These large mucocytes were absent from frozen sections both before and after treatment with alcohol for twenty-four hours. No attempt was made to determine the mode of formation or the origin of the small mucocytes, or the relationship between these and the large mucocytes of Grynfeltt and Pélissier. It seems obvious, however, that whatever their origin the presence of small mucocytes, owing to their frequency in morbid conditions of the brain and cord, is of little importance. On the other hand, the large mucocytes are in my experience much rarer, and may ultimately prove to be of considerable pathological interest.

Myasthenia gravis is a disease whose ætiology is at present unknown. No attempt will be made here to discuss the various pathological and biochemical theories that have been put forward from time to time to explain the curious phenomena so characteristic of the disease. An excellent summary of our present knowledge of the subject will be found in a recent paper by Keschner and Strauss [16]. The most constant pathological changes are collections of small round cells, resembling lymphocytes, in muscles, and certain visceral organs, to which Buzzard [7] gave the name of "lymphorrhages," and an enlargement of the thymus gland, which is hypertrophied or in some cases the seat of a tumour, usually benign. These two findings exist in about half the reported cases, although not always in association. According to the published accounts of the disease, changes in the central nervous system are rare. A number of different observers have noted varying degrees of chromatolysis in the anterior horn cells of the cord. Buzzard, in one of his cases, found a few small collections of lymphocytes in the posterior root ganglia. Mandelbaum and Celler [17] described a lymphocytic infiltration around capillaries in the grey matter near the tenth nerve nucleus and ventral to the olivary body in one case. Barrada [4] laid emphasis on the presence of lipoid granules in the cells, especially of the thalamus and third nerve nucleus. Similar collections of lipoid material, however, are not uncommon in other pathological conditions. The above findings in the nervous system show no uniformity and are so relatively scarce that they can, I think, be safely disregarded in considering the ætiology of the disease.

MYASTHENIA GRAVIS AS A POSSIBLE SEQUEL TO EPIDEMIC ENCEPHALITIS.

Such marked inflammatory and other changes in the spinal cord and brain as were present in this case suggest the possibility of an occasional relationship between epidemic encephalitis and myasthenia gravis. The association between these two conditions has been the subject of a few recent papers, and the case reports will now be considered in detail.

Grossman [10], in a paper entitled "Epidemic Encephalitis simulating Myasthenia Gravis," seems to have been the first person to draw attention to the possibility of this association. He described three cases in which the main symptoms and signs were a sudden appearance of diplopia with ptosis and varying degrees of ophthalmoplegia, dysarthria and dysphagia, an easily induced fatiguability of the limbs, and later the development of paresis and wasting, especially of the proximal musculature of the upper limbs. Two cases showed early bladder involvement and a doubtful plantar response, whilst one case exhibited choreiform movements. Grossman comments on the apparently acute onset of the illness, the lack of variation in the degree of muscular weakness, the absence of a myasthenic electrical reaction and the persistent ophthalmoplegia, as points against the diagnosis of a primary myasthenia gravis. On the other hand, the vesical disturbance and the doubtful plantar response in two of the cases suggested epidemic encephalitis. In one case that came to autopsy there was marked congestion of the vessels in the medulla with lesions of subacute inflammatory nature such as perivascular lymphocytosis and multiple hæmorrhages, most intense in the mid-brain.

Sarbo [22] cites the case of a male, aged 32, who had an attack of epidemic encephalitis in 1920. Bilateral facial paralysis with lethargy lasting five weeks were the principal signs. Subsequently, he developed a rapid fatiguability of all his musculature. This was obvious during every movement, but disappeared if he lay down. The myasthenic electrical reaction was obtained on more than one occasion. No mention is made of the presence or absence of Parkinsonism. Paulian [19] describes a case occurring in a female, aged 29. In December, 1921, she was taken ill with fever and somnolence which lasted two months. This was succeeded by muscular weakness and intermittent diplopia, difficulty in walking, chewing and swallowing. Food regurgitated through her nose. The myasthenic electrical reaction was obtained. She presented the classical picture of myasthenia gravis, and this diagnosis was confirmed by several noted neurologists. She improved for a time, but, whilst abroad, she contracted pneumonia and died. The authors consider that the diplopia and somnolence at the onset pointed to an attack of epidemic encephalitis.

Wimmer and Vedmand [23] report two cases. The first was that of a male, aged 42, who was taken ill in October, 1918, with fever and somnolence. There were no ocular or other symptoms. The condition lasted for about three weeks. Within the next few months he noticed muscular fatiguability, nasal speech and dysphagia, followed by a falling of the lower jaw, which he was forced to support with his hand. In September, 1919, the speech became nearly unintelligible, after reading in a loud voice for one minute. The myasthenic electrical reaction was positive. In 1920, weakness in the arms was noted. He continued at work up till August, 1925, when he was compelled to enter hospital again. He showed atony and weakness of the facial musculature, and especially of the orbicularis oculi, with diplopia due to weakness of the left external rectus. There was atrophy of the masseters and tongue; the latter could not be protruded. Speech was indistinct and at times incomprehensible. There was a slight generalized wasting of the musculature of the limbs with a reduction in power. The faradic and galvanic electrical responses were lost in the masseters and temporal muscles, but no myasthenic reaction could now be obtained. During 1926 the patient improved.

The second case was that of a male, aged 40, who was taken ill with diplopia, muscular fatigue and bulbar symptoms. Somnolence and fever were absent. He improved, and continued at his work until August, 1924, when he noticed that his voice became weak after talking for a time, except in the morning. On examination he showed diplopia, inability to whistle, with marked weakness of the circumoral muscles.

There was no paresis of the vocal cords, but after reading aloud for about twenty minutes his speech became unintelligible. Dysphagia was also present. Motor power in the limbs was practically unimpaired, but fatigue could be easily induced. The deep reflexes were active and the plantar responses flexor in type. There was no myasthenic electrical reaction. The cerebro-spinal fluid was normal. During the next two years there were relapses and remissions in his condition, but in 1926 he was practically well except for an undue fatiguability of his voice. The authors base their diagnosis of epidemic encephalitis in the first case on the initial somnolence and fever. From their description of the cases it would seem possible that in the first case there was an attack of epidemic encephalitis. In the second case there is nothing incompatible with a diagnosis of myasthenia gravis *per se*.

Guillain, Alajouanine and Kalt [12] describe the case of a male, aged 57, who in January, 1925, developed diplopia, which at first was persistent, but later became transitory, appearing especially towards the evening or after fatigue. In October, 1925, variable ptosis, worse always towards the evening, pains in the lumbo-sacral region and fatigue in walking were noticed. Towards the end of a meal mastication became difficult, and there was a certain degree of dysarthria present. He had bilateral ptosis, paresis of the right external rectus and weakness of the masseters. Motor power in the limbs was normal except for a rapid fatiguability. The myasthenic electrical reaction was absent. In addition, the patient showed signs of a slight unilateral Parkinsonism. The second case was that of a male, aged 18, who was taken ill in December, 1922, with diplopia, bilateral ptosis and somnolence, which lasted three weeks. During the following months various myasthenic symptoms developed, such as an abnormal fatiguability of the limbs and masticatory muscles. There is no further note as to the outcome of this case. These authors conclude that in chronic encephalitis muscular weakness may develop, sometimes isolated, sometimes more or less generalized, appearing on or accentuated by muscular effort which closely resembles that seen in myasthenia gravis. Only a careful examination of muscular tonus and the absence of a myasthenic electrical reaction permit a differentiation between the two conditions.

Leenhardt, Reverdiget and Gondard [13] report the case of a boy of 13 in whom Argyll-Robertson pupils, ocular palsies, and double extensor plantar responses and rapid fatiguability of the muscles were noted. This case need not be considered on account of its general lack of resemblance to one of myasthenia gravis.

These few cases can be roughly divided into two groups: (1) Those, in which the clinical picture of myasthenia gravis is well represented, but in which the occurrence of a previous attack of epidemic encephalitis is problematical; (2) those in which there is little doubt that the patient had an attack of epidemic encephalitis, but in which the condition that followed lacked several of the true myasthenic phenomena.

The cases described by Wimmer and Vedmand, and Paulian, would seem to fall into the first group, whilst the remainder correspond to the second group. Three points arise from a consideration of these cases:—

(1) Some of the authors lay stress on muscular atrophy as indicative of an underlying encephalitic infection, but in view of the fact that muscular atrophy is by no means rare in true myasthenia gravis, it is obvious that in this connection this sign should not be relied upon.

(2) In the majority of the case reports no mention is made of the presence or absence of paresis of the facial musculature. Wimmer and Vedmand's first case is an exception. It is well recognized that some degree of facial paresis is usual in the course of myasthenia gravis, the orbicularis oculi being most frequently affected, and therefore an intact facial musculature would be evidence tending to contradict the diagnosis of myasthenia gravis.

(3) Most of the authors lay considerable stress on the presence or absence of the myasthenic electrical reaction first described by Jolly. Although its presence is further diagnostic proof, its absence certainly does not militate against this diagnosis.

In reviewing the above cases it is evident that although there are some grounds for occasionally associating myasthenia gravis and epidemic encephalitis, pathological evidence is at present lacking in support of this.

In Grossman's second case, which came to autopsy, the clinical resemblance to myasthenia gravis, was very slight, the bulbar symptoms being terminal.

No case in the literature has been encountered in which there were inflammatory lesions mainly confined to the cord, and a clinical picture resembling myasthenia gravis such as were found in the present case. The nearest approach to such a case is one described by van Bogaert [5].

A male, aged 35, in December, 1925, first experienced dysarthria towards the evening or after much fatigue; this was accompanied by a feeling of constriction in the throat. Four weeks later these symptoms had become aggravated, and movements of the tongue were now difficult. There was also dysphagia, especially with liquids. The patient also noticed a difficulty in holding up his head, and he became subject to attacks of dyspnœa. When examined in January, 1926, he showed definite atrophy and weakness of the circumoral muscles, tongue, masticatory muscles, and those of the neck. There was no fibrillary tremor, except in the tongue. The palatal reflex was present. Speech was bulbar in type and dysphagia was marked. The eyes were normal. No weakness of the limbs or alteration in the reflexes could be detected. There was no sensory loss on the face or limbs. Between January 1 and February 26, the condition gradually progressed, especially with regard to swallowing, speech and mastication. Paresis of the right arm developed, chiefly affecting the muscles of the hand, which showed commencing atrophy. The facial muscles *in toto* were now affected, and the circumoral muscles were so weak that food was retained in the mouth with difficulty. When examined on March 2, gross atrophy and weakness of the tongue and muscles of the face were noted. The speech was unintelligible. The hands presented the picture seen in the Aran-Duchenne type of atrophy. The deep reflexes were absent in the right arm and feebly present in the left. Walking was still possible, and the deep reflexes were conserved with normal plantar flexion. Death took place on April 17, five months from the onset. The main histological findings were: (1) The third nerve nucleus was normal. There was slight perivascular cuffing in the mid-brain. (2) In the pons many of the capillaries were congested. (3 In the dorsal portion of the medulla small neuroglial nodules were present in the neighbourhood of vessels. Perivascular lymphocytosis was present beneath the floor of the fourth ventricle. The twelfth nucleus, Roller's nucleus, the ventral nucleus of the seventh, and dorsal nucleus of the tenth nerve showed chromatolytic changes of varying severity. In the cord, especially in the cervical region, the vessels of the white matter were infiltrated with lymphocytes and plasma cells to a marked degree. The anterior horn cells were diminished in number; some of them showed chromatolytic changes. Weigert-Pál sections were normal. In the dorsal and lumbar regions of the cord the vascular lesions were less intense than at a higher level, and the motor cells were for the most part normal. The author points out that the pathological findings definitely exclude the diagnosis of an ordinary bulbar palsy, with progression of the disease caudally. He contrasts the localization of the inflammatory lesions in the cervical cord with the definite nuclear changes in the medulla. He describes another similar case in which death had not occurred.

DISCUSSION.

(*a*) *Clinical.*—The clinical picture and course of the disease in the present case were considered typical of myasthenia gravis during the life of the patient. The case was seen by several of my colleagues from the point of view of treatment, and this diagnosis was always confirmed. The question of a possible antecedent attack of epidemic encephalitis was considered in the first instance, but no distinctive symptoms suggesting the acute phase of this disease could be elicited. The histological findings in the cord seemed to throw doubt on the validity of the diagnosis, and therefore the possible relationship of the case to epidemic encephalitis came to be considered. As we have seen, the clinical evidence for a myasthenic type of epidemic encephalitis is not very convincing, but at the same time one or two of the published cases are suggestive in this connection. If epidemic encephalitis does actually produce in some cases a picture of myasthenia gravis, one would have expected an increase in the number of cases of this disease. As far as I am aware, there is no published evidence in support of this view. Turning to the pathological side of the question, what interpretation can be placed on the inflammatory changes in the spinal cord? Assuming for the moment that these may be due to epidemic encephalitis, let us consider the clinical symptoms which may result from involvement of the spinal cord in this disease as proved at autopsy. In the first place, in those cases where the changes are widespread, affecting both brain and spinal cord, there may be no symptoms indicating a downward spread of the disease. In other cases, myoclonic movements and root pains are the expression of the cord lesions, and these symptoms may constitute the greater part of the clinical picture. In a much smaller group are found those cases in which histologically the disease has been practically confined to the cord, and in which the clinical picture is that of a myelitis or neuronitis.

It is evident then that the present case considered from the point of view of epidemic encephalitis does not fall into any previously described clinico-pathological group.

(*b*) *Pathological.*—Marked changes in the muscles and viscera were conspicuous by their absence, except in the case of the thymus gland which showed hypertrophy. If the changes in the central nervous system are to be accorded an important rôle in considering the pathogenesis of the present case, then the hypertrophy of the thymus gland must be considered of little account. Buzzard found lymphorrhages in all five cases of myasthenia gravis which he examined. Their absence in the present case suggests the possibility that we are dealing with a type of myasthenia gravis which differs from the classical form. The importance of a careful examination of the muscles and viscera for lymphorrhages was emphasized by Buzzard; this was recognized at an early stage of the investigation of this case and the portions of muscles were in most instances cut in serial section.

When we come to consider the changes in the cord, the first point to be decided is the nature of the perivascular lymphocytosis. Is this comparable with lymphorrhagic invasion of muscles and visceral organs? The presence, however, of other types of cells besides lymphocytes, such as endothelial and plasma cells, accompanied by over reaction of the neuroglia, definitely points to an inflammatory process. Comparison of the sections with those from cases of subacute encephalitis showed that there was little difference between the character of the cells around the vessels. The significance of mucocytic degeneration which was such a marked feature, not only in the cord but in the brain, has already been alluded to. As far as the evidence provided by the literature goes, chronic epidemic encephalitis shows this form of degeneration more markedly than any other disease. In this connection it may be stated that the process was greater in this case of myasthenia gravis than in any of the cases of chronic epidemic encephalitis which were examined. Van Bogaert's case, referred to earlier in this paper, closely resembles the present one, both clinically and pathologically, except with regard to the muscular atrophy and the chromatolytic changes in the nuclei of the seventh, tenth and twelfth cranial nerves, and in the anterior horn cells of the cervical cord. These findings, which seem interdependent, were absent from my case.

Finally, a study of this case from every angle has forced me to the conclusion that there is a form of myasthenia gravis indistinguishable clinically from the classical type of this disease, associated with inflammatory changes in the cord, which may have a causal relationship.

I am indebted to Dr. J. G. Greenfield for several of the references dealing with the subject of mucocytic degeneration.

SUMMARY.

(1) A case of myasthenia gravis is described in which inflammatory changes in the spinal cord with widespread mucocytic degeneration were found.

(2) The possibility of an occasional relationship between myasthenia gravis and epidemic encephalitis is considered.

P.16268

(3) It is concluded from a study of the case that there is a form of myasthenia gravis associated with inflammatory changes in the central nervous system, the cause of which is at present problematical.

REFERENCES.

[1] Ansalone, G. "Contributo alla istologia patologica della demenza precoce," *Riv. sper. di freniat.*, 1924, **48**, 208.

[2] D'Antona, S. "Sulla genesi della cosi dette zolle di disintegrazione a grappolo," *Rassegna di stud. psichiat.*, 1924, **13**, 501.

[3] Bailey, P., and Shaltenbrand, G. "Die mukose Degeneration der Oligodendroglia," *Deutsch. Zeitschr. f. Nervenheilk.*, 1927, **97**, 231

[4] Barrada, Y. A., and Mott, F. W. "Pathological Findings in the Central Nervous System of a Case of Myasthenia Gravis," *Brain*, 1923, **46**, 237.

[5] Van Bogaert, L. "Étude sur la paralysie labio-glosso-laryngée à évolution subaiguë," *Rev. Neur.*, 1928, **35**, 69.

[6] Buscaino, V. M. "La cause anatomopatologische delle manifestazioni Schizofreniche nella demenza precoce," *Riv. di patol. nerv.*, 1920, **25**, 197.

[7] Buzzard, E. F. "The Clinical History and Post-mortem Examination in Five Cases of Myasthenia Gravis," *Brain*, 1905, **28**, 438.

[8] Ferraro, A. "Acute Swelling of the Oligodendroglia and Grape-like Areas of Disintegration," *Arch. of Neur. and Psych.*, 1928, **20**, 1065.

[9] Greenfield, J. G. "The Pathology of Epidemic Encephalitis," *Journ. of State Medicine*, 1926, **34**, 703.

[10] Grossman, M. "Epidemic Encephalitis simulating Myasthenia gravis," *Journ. of Ment. and Nerv. Dis.*, 1922, **55**, 32.

[11] Grynfeltt, E. "Mucocytes et leur significance," *Compt. Rend. et Mém. de Soc. de Biol.*, 1923, **89**, 1264.

[12] Guillain, G., Alajouanine, Th., et Kalt, M. "La forme myasthénique de l'encéphalite épidémique prolongée," *Rev. neurol.*, 1926, **33**, 39.

[13] Leenhardt, Reverdiget et Gondard. "Un cas de myasthénie postencéphalitique," *Bull. de la Soc. de Sci. Méd. de Montpelier*. 1927, **5**, 226.

[14] Lhermitte, J., et Radovici, A. "Étude sur la dégénération basophile metachromatique dans l'encéphalite épidémique," *Compt. rend. de la Soc. de Biol.*, 1921, **84**, 981.

[15] Lhermitte, J., Kraus, W. M., and Bertillon, F. "Mucin-like Bodies in the Central Nervous System in Epidemic Encephalitis," *Arch. of Neur. and Psych.*, 1924, **12**, 620.

[16] Kescher, M., and Strauss, I. "Myasthenia Gravis," *ibid.*, 1927, **17**, 337.

[17] Mandelbaum, F. S., and Oeller, H. L. "A Contribution to the Pathology of Myasthenia Gravis," *Journ. of Exper. Med.*, 1908, **10**, 308.

[18] Pagès, M., Bénoit et Pélissier, G. "La dégénérescence mucocytaire de la Nevroglie," *Languédoc Médical*, 1926, **9**, 1.

[19] Paulian, D. E. "Considérations étiologiques sur la myasthénie et ses relations avec l'encéphalite épidémique chronique," *Rev. Neurol.*, 1926, **33**, 368.

[20] Pélissier, G. "Syndrome Wilsonien consécutif à la névraxite épidémique," *Thèse de Montpelier*, 1924.

[21] Salustri, E. "Sulle cosi dette zolle di disintegrazione a grappolo," *Rev. sper. di freniat.*, 1924, **48**, 255.

[22] Sarbo, A. "Ueber die Encephalitis epidemica, auf Grund der Erfahrungen der Epidemie von 1920," Abst. *Zeit. f. d. ges. Neur. u. Psych.*, 1921, **27**, 509.

[23] Wimmer, A., et Vedmand, H. "Le syndrome myasthénique dans l'encéphalite épidémique chronique," *Rev. Neurol.*, 1926, **33**, 368.

ARTERIOSCLEROTIC PARKINSONISM.[1]

BY MACDONALD CRITCHLEY.

CONTENTS.

		PAGE
CHAPTER I.	INTRODUCTION	23
CHAPTER II.	HISTORICAL	25
CHAPTER III.	SYMPTOMATOLOGY	32
CHAPTER IV.	MORBID PHYSIOLOGY	57
CHAPTER V.	PATHOLOGY	64
CONCLUSIONS ..	.. ..	78

CHAPTER I.—INTRODUCTION.

HITHERTO scant attention has been paid to the occurrence of Parkinsonism among the syndromes of cerebro-vascular disease. It is the object of this paper to emphasize the importance of this syndrome as being one of the most frequent objective manifestations of a protean disease. By the term Parkinsonism is here understood a condition of general rigidity of non-pyramidal type, with weakness and slowness of movement—in fact, a symptomatic variety of paralysis agitans such as one associates with disorder of the pallidal system. As we shall see, so-called "neostriatal manifestations" of the nature of athetosis, tremor, or chorea play little or no part in this variety of Parkinsonism.

It is not essential, nor indeed is it usual, to find the Parkinsonian syndrome in its entirety in cerebral arteriosclerosis. Incomplete forms are more common; thus one patient may show a generalized rigidity, another a poverty of spontaneous movement, and another a mask-like facies or bradykinesis. Cerebral arteriosclerosis is, however, a progressive malady and the clinical picture may change rapidly so that various incomplete forms often merge into an identical state of complete Parkinsonism.

The importance of this syndrome becomes evident when it is shown to take part in syndromes as diffuse as Marie's "état lacunaire," pseudobulbar palsy, cerebral meiopragia (Claude and Cuel [15]), "arteriosklerotische Muskelstarre" (Foerster [25]), and many of the organic psychoses. Parkinsonism of greater or lesser degree may be regarded as a common multiple, participating in syndromes of the utmost diversity.

---

[1] Work carried out at the National Hospital, Queen Square, with the assistance of the Medical Research Council.

The relationship between arteriosclerotic Parkinsonism and "senile" or "idiopathic" paralysis agitans is not easy to define, but there are certain clinical and pathological points of differentiation between them, as there are between the idiopathic and post-encephalitic varieties. A study of the literature and a wide experience of cerebral arteriosclerosis of all types make it obvious that many cases of symptomatic Parkinsonism would at first sight be relegated to the "idiopathic" group, and, secondly, seem to indicate that there is no sharp distinction between the so-called idiopathic and symptomatic types. The more detailed the clinical examination and the closer the study of the disease the narrower becomes the category of "idiopathic" paralysis agitans.

The trend of modern thought is to regard Parkinsonism as a syndrome rather than as a disease; such was the opinion of Souques [90 in 1921, when he said: "Paralysis agitans or Parkinson's disease is not in my opinion a disease-entity. I picture it as a syndrome common to different causes acting upon the same part of the brain. The important factor is not so much the nature of the cause as its site—not so much the variety of the lesion as its topography." Again, Foix and Nicolesco [25] adopt the same standpoint: "There are no absolute frontiers between Parkinson's disease—so-called—and the pseudobulbar Parkinsonism of the aged. There is no doubt in our mind that we will more and more place into their true category (i.e., Parkinsonism) certain symptoms of that type often met with in the aged."

Foerster's description of arteriosclerotic rigidity appeared in 1909, and it is obvious from his clear account that he was describing a variety of hypertonus which fulfils many of the requirements of so-called extrapyramidal rigidity. Other factors are present, however, which contribute to the state of increased tonus, but the basis is a pallidal type of rigidity. Foerster remarks on the close analogy with paralysis agitans, and suggests the possibility of an identical location of the disease. In the absence, however, of a sure anatomical basis, he writes in his concluding paragraph, "I must content myself for the present with describing this particular disease-picture as arteriosclerotic rigidity."

Although the arteriosclerotic varieties of Parkinsonism have not received widespread recognition, the symptomatic varieties resulting from vascular disease of syphilitic nature are well known. Mesencephalitis syphilitica (of Kinnier Wilson and Cobb) is an example.

The conception of a pallidal type of arteriosclerosis is familiar to continental writers, but in this country it is scarcely ever specifically mentioned, although possibly a matter of common experience. James [43] has described many of the Parkinsonian symptoms which occur in the late stages of severe cerebral arteriosclerosis, and he quotes Mott as saying that cerebral arteriosclerosis may be confused clinically with the sequelæ of encephalitis lethargica. The writings of C. and O. Vogt, Jakob, Steck, Lhermitte and his collaborators (to quote only a few) testify to the continental recognition of pallidal syndromes or arteriosclerotic origin. Souques has classified the clinical types of Parkinsonism as follows :—

(1) Presenile or senile Parkinsonian syndromes: (*a*) typical; (*b*) sine agitatione; (*c*) sine rigiditate.

(2) Juvenile Parkinsonian syndromes.

(3) Parkinsonian syndromes due to presenile lesions of the corpus striatum.

(4) Parkinsonian syndromes due to macroscopic focal lesions (e.g., lacunes).

(5) Post-encephalitic Parkinsonian syndromes.

The varieties included by Souques in his third and fourth categories are those which come within the scope of this paper.

Regarded from another angle this paper is intended as a contribution to recent studies in psychiatry wherein neurological features are studied in relationship to various psychoses. In association with the clinical and pathological studies of striatal factors in dementia præcox (Farran-Ridge [23], Stoddart [93], Reiter [87], Wladyezko [105]), in general paralysis (Steck [91]), in manic-depressive insanity (Urstein [96]), in Alzheimer's disease (Stief [92]), the problem of the involvement of the basal ganglia in senile and arteriosclerotic dementia merits attention.

CHAPTER II.—HISTORICAL.

The varieties of arteriosclerotic Parkinsonism do not permit of a sharply defined clinical classification. Such types as exist merge one into another, and in several instances the differences are in degree rather than in character. But for the sake of clarity and convenience in description it is advisable to attempt a classification. The following five varieties may be isolated :—

Type 1—characterized by rigidity, fixed facies, and short-stepping gait.

Type 2, as in Type 1, with the addition of pseudo-bulbar manifestations (dysarthria, dysphagia, spontaneous laughter and crying).

Two sub-types can be recognized: (*a*) cases with signs of pyramidal disorder, (*b*) cases without signs of pyramidal disorder.

Type 3 as in Type 1, but with the addition of dementia, and incontinence of urine and fæces.

Type 4 as in Type 1, with signs of pyramidal disease but without pseudo-bulbar manifestations (=mixed pyramido-pallidal syndrome).

Type 5 as in Type 1, but with the super-imposition of cerebellar symptoms (=mixed pallido-cerebellar syndrome).

It is obvious that a certain amount of overlap is unavoidable if the above classification is adopted. Thus, in Type 2 there may be signs of pyramidal disease, and in addition some degree of dementia and incontinence may be present.

The first type, which may be regarded as the mildest variety of Parkinsonism, is perhaps the commonest. As a rule the syndrome does not cause much incapacity, hence instances are encountered socially rather than professionally. Frequently the only symptoms are hyperpietic in type and the patient comes under observation for headache, giddiness, defect of memory, or frequency of micturition. Many of the patients described by Marie as "lacunaires" come into this group. Some of the severer examples would be included within Foerster's description of arteriosclerotic rigidity. Collins [78] (1906) refers to this type in his paper on "a definite variety of cerebro-vascular disease." In his series of 135 cases of arteriosclerosis this particular syndrome was present thirteen times. He also refers to a case reported by Pickett [78], of a man of 67 who had gradually become "stiff all over" in the course of two years. There was no mental enfeeblement; sphincter control was perfect; but the speech was "mumbling." A particular case had been described by Collins [16] himself in the previous year: A woman of 50 gradually changed in character and became subject to frequent local epileptic spasms confined to one hand. There was no paresis but a definite absence of elasticity or grace in her movements . . . "her appearance and attitude reminding one forcibly of Parkinson's disease." There were no changes in the reflexes.

The following case exemplifies the characteristic features of the first type:—

J. P., male, aged 66, came to the National Hospital (Dr. Walshe) because of difficulty in walking. For two and a half years he had gradually become uncertain on his legs, and complained of a tendency to fall backwards. He noticed also that he was becoming slower in his movements. Examination revealed a well-nourished old man with a fixed and expressionless face. His attitude was statuesque and there was an obvious poverty of spontaneous movement; speech was a little monotonous and not well articulated. There was no psychical change. A generalized rigidity was noticeable in the trunk and extremities; muscular strength was good but all movements were performed slowly. Tremor was not present. All the tendon jerks were brisk; the plantar responses were flexor in type; no clonus was obtainable. When walking the patient held himself stiffly, swung his arms awkwardly at the shoulders, and took very short shuffling steps. Blood-pressure was 218/105; the radial arteries were thickened, and the retinal arteries were tortuous and indented the veins. The second aortic sound was ringing.

Some of the cases recorded by Lhermitte [54] and [55] and by Verger [97], belong to this clinical group. Van Gehuchten's case [34] was similar but differed in the suddenness of onset. In Signorelli's patient [89] there was also a nystagmus of the palate, pharynx and vocal cords.

The second category includes those patients who show, besides the features characteristic of Type 1, manifestations of a "pseudo-bulbar" nature. The clinical picture is in fact that of a double hemiplegia, with or without a history of successive strokes, but with definite manifestations of a Parkinsonian nature. In a proportion of cases, probably in the majority, the Parkinsonian traits have been masked by the more obvious paretic signs, and have consequently not been directly emphasized. It is probable, too, that in the past some of these patients have been regarded as instances of "paralysis agitans with bulbar symptoms." (cf. Ashley Mackintosh [69]; Janischewsky [44].)

This group may be further subdivided according as to whether signs of pyramidal disease are demonstrable or not. In those cases which are sometimes tersely though inaccurately termed "double hemiplegics," Babinski responses, ankle clonus, and signs of pyramidal spasticity reveal a state of bilateral pyramidal disease. The majority of these have few Parkinsonian signs. Where a pseudo-bulbar syndrome exists without signs of pyramidal affection, the Parkinsonian manifestations are usually more obvious. The onset is usually gradual and there is frequently no history of a stroke. Typically, the patients in this group show no mental enfeeblement, though their emotivity may give rise to a false impression of childishness. In severer cases, however, some degree of dementia is present, and the case merges gradually into Type 3.

This particular syndrome was first commented on specifically by

Brissaud [9] (1895), as a characteristic clinical variety of senile softening. After detailing the features common to paralysis agitans and to the pseudo-bulbar syndrome, he pointed out the Parkinsonian attitude and physiognomy and described a short-stepping gait, slow and uncertain movement as commonplace features with subjects who had sustained numerous small softenings of thrombotic origin.

As an example of the type of patient included within Group 2 the following case may be quoted :—

B. T., female, aged 51, was admitted to the National Hospital (Dr. Holmes) for giddiness. Symptoms of general weakness and difficulty in walking had been present for eighteen months. She was dull mentally and emotionally very unstable. The speech was dysarthric. Her face was staring and immobile. There was no local paralysis; the tendon jerks were increased and the plantar responses were indefinite. All her movements were slow and there was an universal rigidity. She had some difficulty in swallowing fluids. Walking was a matter of great difficulty and was characterized by extremely small shuffling steps. Blood pressure was 225/130; the radials were hard and tortuous; the second aortic sound was accentuated. Blood urea 30 mg. per cent.; non-protein nitrogen 24·5. She was seen one year, and again eighteen months later in an Infirmary; her physical signs were as before, with the addition of some degree of facial apraxia and over-reaction on emotional movements.

Numerous similar cases could be quoted from the literature. Cases R. E. and A. R. recorded by Holmes [38] belong to this category, but in these instances tremor was also present. A patient reported by Lemos (and afterwards pathologically by C. and O. Vogt) was described by him as suffering from a "paralysie pseudo-bulbaire Parkinsonienne." Other cases include those of Noethe [74], Monier-Vinard and Dalsace [71], Lhermitte and Cornil [57], Claude and Alajouanine [14], Verger [97], and Urechia, Mihalescu and Elekes [95]. All seven of Kashida's patients [46] and three of Kleist's (Nos. 1 and 6 [47] and No. 6 [48]) belong to this category.

Type 3 includes patients who present, in addition to Parkinsonian features, some degree of mental deterioration and incontinence of urine and fæces. The psychical changes range from simple retardation and defect of memory to the grossest varieties of global dementia. Sphincter disorders are always present, varying from the occasional lapses due to inattention to a complete lack of control over the excretions. A proportion of the patients in this category have signs referable to disordered bulbar function, but these are slight when compared with the preponderating psychical defects. Evidences of unilateral or bilateral pyramidal affection are not rare, but they are slight and unessential in this particular syndrome.

Rowland (1851) [84] probably referred to this type when he wrote of the restless and demented arteriopath: "There is a species of mental imbecility sometimes accompanying cerebral softenings, which is manifested chiefly in the manner and actions, and on that account is called by the French physicians "délire d'action." . . . From this state they generally pass into more determined dementia, in which the mind is hopelessly clouded, the expression vacant and idiotic, while, at the same time, the extremities are paralytic."

The following case illustrates the main clinical features characteristic of the third type :—

H. C. H., male, aged 72, was seen on several occasions at St. Pancras Infirmary. No history was obtainable. His mental state was one of profound dementia with occasional ideas of persecution and auditory hallucinations. He was doubly incontinent, and, noisy and troublesome at night. The physical state was characterized by generalized rigidity. He lay stiff and immobile, with his head off the pillow. There was no spontaneous speech and his replies were unintelligible. There was no lack of muscular strength but the patient seldom moved; passive manipulations revealed a definite hypertonus. A tendency towards the assumption of catatonic attitudes was noticeable. The tendon jerks were depressed and the plantar responses were equivocal in type.

Numerous other examples could be quoted from the literature, as the cases recorded by Cones [18], Reich, Martini and Isserlin [68], Pinéas [79] and [86], Stief [92] (Cases 1-5), and Urechia, Mihalescu and Elekes (Case 3). Many of Merzbach's [70] patients fall into this class, in particular his sixth and tenth cases.

Type 4.—Within this group are included cases in which physical signs of pyramidal disease, as bilateral extensor plantar responses and clonus, accompany those of pallidal origin. It is important that in contradistinction to the cases of so-called double hemiplegia and pseudobulbar palsy, dysphagia, dysarthria, and forced laughter and crying do not appear. This type of syndrome was familiar to Lhermitte under the title of "progressive pyramido-pallidal degeneration," and is now spoken of as "Lhermitte's disease." In his 1922 paper he gave an excellent example : A man aged 45 developed rigidity of the left arm and later of the left leg ; his face was fixed and his trunk and extremities were intensely rigid. There was a relative akinesis with great slowness of movement. Later some dysarthria and speech difficulty appeared.

According to Lhermitte, the characteristics of the pyramido-pallidal syndrome are as follows:—

(1) Gradual onset and slow progression.

(2) A degree of hypertonus greater than in the ordinary pseudo-bulbar palsy, and rigidity combining the features of pyramidal with those of extrapyramidal disease.

(3) A Parkinsonian attitude of the hands.

(4) Slowness of movement, with a relative conservation of muscular force.

Lhermitte also includes pseudo-bulbar manifestations among the characteristic signs, but I do not consider these an essential feature of the syndrome.

As the disease progresses the pyramidal features may advance and overshadow the pallidal manifestations. The terminal stage is one of absolute helplessness. In a case recently seen in Professor Lhermitte's service at the Hôpital Villejuif there was a state of complete flexor quadriplegia, with contractures and emaciation; speech was impossible and swallowing was a matter of extreme difficulty. Consciousness was unimpaired and there was no emotivity.

Similar cases have been recorded by Lhermitte, Cornil and Quesnil, Buzzard and Barnes [12], and Lhermitte and McAlpine [61].

Type 5.—The conception of a clinical syndrome of vascular origin, combining the features of striate involvement with those of cerebellar disease, is by no means new. The so-called cerebellar types of pseudo-bulbar palsy illustrate this combination, and although but few exact pathological data are available, the clinical aspects have been long familiar.

One of the earliest cases described was by Raymond and Alquier [80]. Other instances have since been recorded by Garbini and Rossi [32], Lhermitte and Cuel [59], Sicard and Paraf [88], Crouzon, Dereux and Kensinger [20], Orzechowski [75] and Kleist (Case 7).

In 1927 and 1928 Freund and Rotter [29] and [30], in their papers on the extrapyramidal disturbances of movement in old age, described eight cases with autopsies. In four and possibly five (Nos. 1, 4, 5, 6 and ?7) lesions were found in the dentate nuclei, the olives and in the brachium conjunctivum, in addition to the typical vascular lesions in the striatum. Apparently these patients exhibited during life none of the manifestations ordinarily regarded as cerebellar, and they would clinically be relegated either to our first or third clinical group. The authors comment upon the remarkable pathological findings in their fourth, fifth and sixth cases, and they regard them as examples of a peculiar type of strio-pallidal-dentate-rubral-peduncular system disease, hitherto undescribed.

The following case has been chosen to illustrate this particular type:—

H. B., male, aged 57, was admitted to the National Hospital (Dr. Collier), for pains and weakness in the legs which had been present for three years. His speech had gradually become indistinct. For about twelve months he had staggered while walking. Examination revealed a feeble man of subnormal intelligence. Articulation was slurred and there were recognizable traces of echolalia. Muscle tone was everywhere increased; the reflexes were exaggerated and the plantar responses doubtfully extensor in type The motor power was good, but he was very inco-ordinate in his actions, and an intention tremor was demonstrable in both arms. There was nystagmus on lateral ocular deviation. The gait was propulsive and marked by very small steps. He was incontinent of urine and fæces. The blood-pressure was 220/130; the peripheral arteries were markedly sclerosed.

In a group apart we may consider those cases which are sometimes spoken of as "senile Vorsteifung," or Jakob's disease. The clinical picture resembles that of Type 3 in presenting a state of general rigidity and hypokinesis with dementia, but there are three main points of distinction: in the first place the mental symptoms may antedate the physical manifestations by a long period; secondly, the age of onset is later than in the majority of cases belonging to Type 3; thirdly, the evidences of arteriosclerosis may not be obvious and the blood-pressure is usually low. Few cases of this syndrome have been recorded, although its occurrence is well recognized in all institutions for the aged. Jakob, in his monograph on extra-pyramidal disease, gives a photograph of an illustrative case (Abb. 65) [42]. Although he gives no clinical particulars, the pathology of the syndrome is treated in detail.

A case recorded by Lemos in 1913 falls within this category: his patient—a 100-year-old negro—showed during the last few years of his life a bowed statuesque attitude; there was some tremor of the arms; he walked with small steps, and with some tendency towards propulsion. When turning he moved in one piece. His brain was afterwards studied by C. and O. Vogt.

The eighth case recorded by Freund and Rotter was regarded as one of Jakob's disease. Their patient, a female aged 77, became agitated and restless during the last five years of her life. She was slightly delirious at night. Three months before her death she became profoundly disorientated, and her agitation grew worse. Her gait was stiff; there was but little hypertonus beyond a slight resistance to passive manipulations of the right leg. The reflexes were normal. Later, other symptoms appeared, such as echolalia, agnosia, motor apraxia and agraphia.

Syphilitic vascular Parkinsonism.—The possibility of a Parkinsonian syndrome due to pure vascular lesions of a sclerotic type is still further suggested by the paralysis agitans-like conditions secondary to syphilitic disease of the cerebral arteries. Such cases form a very well-known clinical entity which has been described for many years under various titles—tabes with paralysis agitans, syphilitic paralysis agitans, tromo-paralysis tabetiformis, mesencephalitis syphilitica, "striatite syphilitique primitive." The symptomatology has been adequately discussed and the syndrome put upon a sound basis by the recent work of Kinnier Wilson and Cobb [104], and later still by Wohlfahrt [106]. Pathological study of this type of syndrome has been forthcoming in only a few instances. C. and O. Vogt found in the brain of a man with paralysis agitans and bilateral Argyll-Robertson pupils an "état lacunaire" in the striatum and pallidum. The papers of Urechia [94], Mella and Katz [69] and Lhermitte [56] have also contributed to our knowledge of its pathology.

CHAPTER III.—SYMPTOMATOLOGY.

The clinical manifestations of the arteriosclerotic varieties of Parkinsonism resemble in no little degree those of idiopathic paralysis agitans; there are, however, some distinctive features in their symptomatology and also certain additional manifestations which are not found in the idiopathic cases. For this reason the clinical aspect will be discussed somewhat fully. It must be emphasized that individual patients show marked differences in the degree of affection, so that in the slighter cases there may be but few of the characteristic symptoms; on account of the comparatively rapid course of the disease, however, it is important to recognize the clinical manifestations of all stages.

The stance and attitude of these patients are so characteristic that an immediate diagnosis is often possible. There is a peculiar lack of mobility, so that the body moves as a whole without the play of the individual limbs or segments.

A mask-like fixity of the face is typical. It is incorrect, however, to describe the appearance as "expressionless," for the face in repose is full of emotional significance; as Hughlings Jackson has emphasized, a more accurate description would be to speak of the expression as fixed the lines of the face are carved into an image which does not change with the passing mood. As a rule the expression is one of bewilderment, as portrayed by the elevated brows, the retracted lids and the gaping mouth. Nearly eighty years ago Rowland [84] commented upon the facial expression in cases of confirmed cerebral softening . . . "In old chronic cases that mixture of imbecility and astonishment which is so justly held to portray the disease is strongly impressed upon the features." The face immediately lights up upon appropriate stimuli, volitional or emotional. It is then apparent that there is no defect in the range of movement during the acts of showing the teeth, or screwing up the lids. Nor, in the early stages at least, is there any delay in the initiation of the movements or slowness in their execution. On the contrary, it is not rare to find an exaggerated play of facial movement during voluntary activity; in such a case the act of showing the teeth is executed with startling promptness, the lips are retracted to the widest possible extent, and may be accompanied by associated extraneous movements, with grimace-like effects. Emotional movements are also full in range and prompt in initiation and execution; in some cases, particularly when some degree of emotional instability occurs, there is a similar exaggerated facial activity. In other instances there may be an apparent dissociation between the individual facial movements, so that, for example, in the act of smiling, the lower half of the face alone moves, the upper portion remaining immobile—the so-called "adiadochokinèse de la mimique" (Steck).

It is noteworthy that there is usually no excessive sebaceous secretion, so that the facial greasiness of the ordinary Parkinsonian is not observed. Neither does one see the smoothing-out of the wrinkles which so often tends to produce an illusion of youth and belies the years of the Parkinsonian.

The head and neck are held upon the shoulders in an attitude of relative immobility; there is an absence of the quick lateral movements of the head seen in normal individuals; when the patient wishes to alter his direction or to look to one side, the head, neck and shoulders move in one piece and the movement is not broken down into its components. In early cases the stance is more erect than in the true Parkinsonian. When the patient walks, his neck and trunk are straight and his arms swing from the shoulders. The movements of the arms, however, are not entirely normal; they are often held rigidly away from the sides with the elbows partially flexed, so that the associated movement takes place at the shoulder-joints and not, as in the normal, at both shoulder and elbow.

When the patient is observed in bed, there is often a characteristic attitude of the head, the neck being slightly flexed, so that the occiput is held in the air unsupported by the pillow. Such an attitude—the "psychical pillow"—is not uncommon in many of the organic psychoses.

One of the chief clinical characteristics of the arteriosclerotic forms of Parkinsonism is seen in the gait. There is no excessive flexion of hip and knee as in paralysis agitans; at the knee-joint there is little or no flexion, and only the slightest bending at the hip; the steps are exceptionally short; one toe is usually advanced in front of the other no further than six inches, and often less. In the earlier stages the feet do not shuffle along the ground, but later they are no longer lifted. The trunk is not bent forward and the centre of gravity lies well above the base; festination and propulsion are, therefore, not seen. There is no widening of the base and no trace of inco-ordination. When the patient halts the stance is steady, without swaying or tendency to retropulsion. The characteristics of this gait are, therefore, those of the well-known "marche à petits pas," originally described by Dejerine, and associated by Marie and his school with the condition of progressive lacunar disintegration.

Sometimes a more flexed attitude of the trunk and limbs develops as the disease advances, while the onset of vertigo may influence the gait, causing the patient to sway while walking. Sometimes he is unable to remain in an erect attitude but sways backwards and falls. In such cases the muscles of the patient's foot contract forcibly in an attempt to steady the trunk, and the toes may be seen to become plantar-flexed in an effort to grasp the ground. Catola [13], who described this feature, spoke of the "claw-toes."

When the patient mounts or descends a flight of stairs the characteristic short-steppage elements are no longer apparent and the movements approximate more closely to the normal. If he goes up a slope the gait is less disturbed, but in descending an incline there is much difficulty and the steps become shorter and the progression is cautious and hesitant. Sometimes, through fatigue or nervousness, the patient, after taking a few steps, abandons his attempts at walking and seeks support, but with encouragement he is readily persuaded to continue. This modification of the ordinary "marche à petits pas" is sometimes known as "Petrén's gait."

Turning movements are carried out slowly and stiffly, the feet taking small steps. At first glance the head, neck and trunk seem to move as a single unit, but on close examination it can be seen that the movement is decomposed into its constituent phases as in the normal individual, though each component movement is slow and minimal in degree. The arms are widely abducted as if the patient, anticipating a fall, were seeking support.

The patient moves from the erect to a sitting posture only with difficulty and with great slowness. In advanced stages this is impossible without assistance. A similar difficulty is experienced in getting up from a chair. At a late stage in the disease he may be quite unable to stand even with assistance.

Muscle tone.—It may be stated at the outset that there is usually some degree of hypertonus present, but it is uneven in distribution and variable in degree. This type of rigidity differs clinically from that associated with disease of the motor systems, and hence falls into the category neither of pyramidal nor of ordinary extrapyramidal rigidity. Moreover, there is an obvious relationship between the degree of hypertonus and the psychical activities of the patient, as evidenced by his power of attention, his ability to concentrate and his cerebration rate. A tendency towards the assumption of prolonged catatonic postures is an especial feature of this variety of hypertonus.

The rigidity is greater in the limbs than in the trunk, in the lower extremities than in the upper, and in the proximal parts of the limbs than in the distal. Thus, in the arms there is an obvious resistance to passive manipulation of the shoulder-joints, and a similar, though slighter, stiffness at the elbows. Passive extension of the fore-arm is more difficult than flexion and, indeed, in the severer cases, full elbow extension may be impossible. Usually there is little or no increase of tone at the wrists or in the phalanges, and the fingers can be bent back through a normal range by passive movement.

Though rigidity is slight or absent in the distal segments of the upper limb, the hands tend to assume abnormal postures which, however, can be passively corrected. Thus the fingers often remain extended at the interphalangeal joints, but are flexed upon the metacarpals, and the thumb is adducted. The terminal phalanges may actually show a hyperextension. Later the fingers and thumb become flexed and a "paw-like" attitude slowly results. The wrist is usually flexed and deviated to the ulnar side, the fore-arm pronated and the upper arm slightly abducted and internally rotated. It is important to realize that in the early stages these attitudes are readily altered by active or passive efforts, and appear to arise independently of contractures. Foerster [26] speaks of a specific flexing factor as responsible for the assumption of these characteristic postures.

A much greater degree of rigidity is always apparent in the legs. Both lower limbs are hypertonic but one leg may be more rigid than the other. Until the later stages, the attitude of the legs is that of extension, the feet lying in the equinus position. Adductor spasm is always present, and when one leg is picked up off the bed the opposite limb at once adducts to take up a position on the other side of the midline of the body. In bedridden patients, a characteristic attitude of the lower limbs may develop; one leg may be internally rotated and adducted, while the other limb is rotated outwards and abducted. The feet tend to become hollowed, though the high-grade deformities seen in severer states of pyramidal disease are rare.

Vigorous passive manipulation of the head on the neck and upon the shoulders usually betrays some increase of tonus, though the rigidity is rarely as great as in the legs. Similarly, passive movement of the trunk in all directions is resisted by some degree of hypertonus.

The nature of the rigidity differs from the more usual clinical varieties in several aspects: first, there is no approximation towards a a "clasp-knife" type of spasticity; in other words, the resistance encountered during passive flexion of a given joint is the same in all phases of the movement, and is no less at the end of the excursion than at the commencement. Neither do we encounter a cogwheel or punctuate type of hypertonus; the rigidity resembles rather that met with in paralysis agitans *sine agitatione*, in being "sticky" or "lead pipe" in character. It is constant in degree for all phases of a passive movement. Foerster speaks of the rigidity as being waxy. Secondly, the degree of rigidity does not lessen with repeated manipulation, unlike the spasticity of pyramidal disease, which tends to wear off with repeated forceful manipulations. Thirdly, the resistance is not the same in all movements of a given joint; thus it will be found harder to flex than to extend the knees, to straighten the elbow than to bend it. In this respect, the rigidity resembles that of pyramidal disease, and also (though to a minor degree) that of extrapyramidal affections. Fourthly, the rigidity is variable in degree. This is perhaps the most obvious feature and is one which gives the impression, on superficial or cursory examination, of a failure to relax on the part of the patient. To some extent, the amount of rigidity varies according to the force used in the passive manipulation; thus, at times vigorous movement of the limb seems to be opposed by an equally vigorous resistance, whilst manipulations of less force appear to reveal a lesser degree of rigidity.[1] In this way there is a surface resemblance to hysterical hypertonus. The analogy must not be laboured, however, for other factors are traceable which influence the amount of rigidity. It is apparent to all observers that there is a great difficulty in obtaining satisfactory relaxation on the part of the patient. He usually behaves in one or two ways: either he is over-anxious to co-operate, and tries to assist the examiner by making active movements of a similar kind, or, more usually, he tends to adopt a resistive attitude and to tighten his musculature with a determination which is almost purposeful. To overcome this difficulty in relaxation and to eliminate any volitional factor, many devices may be found necessary. The patient's attention may be distracted by engaging him in conversation; it is a mistake to set him a mental calculation because, as Golla [36] has shown, abstract mental effort is attended by a slight increase in tone. The most successful measures require the intervention of a third party who will distract the patient's attention by talking to him or by examining some other part of the body. By one or other of these means it is usually possible to remove the personal element of error. But, when full relaxation has been obtained, a *marked degree of hypertonus still remains.* It may be said, therefore, that although the arteriosclerotic type of rigidity is characterized clinically by a difficulty in obtaining relaxation, it is, nevertheless, independent of the voluntary factor and still exists when all the elements of volition are removed.

The clinical manifestations of arteriosclerotic rigidity have been treated in detail by Kleist [49] under the term "Gegenhalten" (appropriately translated by Selling as "counterpull"). By "Gegenhalten" Kleist refers to the tonic contraction—manifest or latent—which can be brought out by passive movement of various parts of the body. It may be reactive (i.e., directed against passive manipulations) or spontaneous; it may be universal or local, and in the latter case it tends to be present in certain predilected parts, as the elevators of the jaw, the neck muscles, the trunk, the proximal limb segments and the adductors of the arms and hips.

Foerster lays emphasis on the existence in these cases of a phenomenon which he terms fixation-contraction ("Fixations-spannung"). If the points of insertion of a muscle are approximated to their fullest, and if the limb is held in that position for a moment before releasing it, the shortened muscle contracts forcibly and maintains the shortening for a time. Consequently, the limb remains in its new position and can only be extended by exerting a great deal of force. Although a similar phenomenon occurs in pyramidal disease, Foerster believes that fixation-contraction is stronger and more quickly elicited in states of arteriosclerotic rigidity. It is immaterial, according to Foerster, whether the points of insertion of the muscle are approximated by activities of a volitional, automatic, or reflex nature, or even by electrical stimulation. In every case an identical fixation-contraction will result.

---

[1] Foerster, on the other hand, has described a directly opposite phenomenon; he states that in many cases the resistance can be overcome by gentle manipulation rather than by sudden or brusque movements.

A certain degree of rigid fixity is present in the advanced stages of the disease, so that passive movement of one body segment becomes associated with a simultaneous and involuntary movement of another segment. Thus, passive dorsiflexion of the foot is accompanied by an immediate flexion of the knee and hip joints. If the patient's head is passively bent forwards on to the chest while he is lying supine, there is an associated flexion of the legs.

Palpation of the muscles themselves may reveal an abnormal hardness. This statement is especially true of the older patient. The distribution of this muscle hardness is not universal, however; when present it always occurs in the legs, while the muscles of the trunk and upper extremity are almost always of normal consistency to palpation. Associated with this increased firmness, one usually encounters an exaggerated mechanical irritability. The muscles may be bulky, but in the severer grades of cerebral arteriosclerosis the subject is often of spare build and meagre muscular development. In uncomplicated cases no fibrillation occurs, but it is actually not a rare finding, due possibly to concomitant spinal lesions of vascular origin. Electrical stimulation of the muscle produces a slow contraction which tends to persist for a little after the cessation of the stimulus; the relaxation is slow and gradual.

Attention has often been called to the striking visibility of the rigid musculature. Owing to the hardness of the muscular bellies and to their permanent state of increased tension, the muscular conformity of the limbs is frequently exaggerated. In the female subject, the contours may approximate to the masculine type. The tendinous insertions are tense and stand out clearly at the joints.

By employing various manœuvres it is possible to alter temporarily the degree of hypertonus. According to Foerster, the rigidity is increased by cold and is reduced by passive congestion, as by compression of the limb with an Esmarch's bandage. I have not been able to confirm the latter observation, for I found no objective change in the degree of rigidity after or during the application of a tourniquet. Warmth exerts a very definite influence upon the muscle tonus; if the lower limbs are placed in a radiant heat bath for ten to twenty minutes an obvious decrease in the rigidity results. Immersion in a hot water bath has a similar effect. The decrease is purely temporary, however. The action of heat in reducing tone in arteriosclerotic rigidity is similar to its effect on spasticity due to pyramidal or extrapyramidal disease.

Liljestrand and Magnus [62] have shown that in decerebrate preparations the rigidity can be abolished locally by the intramuscular injection of novocain in doses too small to affect either the indirect faradic excitability or the reflex activities. Walshe has employed this method in his investigation of the rigidity in paralysis agitans. By de-afferenting a particular muscle with an injection of novocain near its motor point, the rigidity is temporarily abolished. An identical technique was employed by me in cases of arteriosclerotic rigidity. Novocain was injected into the deltoid muscles of patients in whom passive movements at the shoulder-joints revealed a high degree of rigidity. The injection resulted in a partial reduction of the hypertonus; although complete flaccidity was not produced, the diminution in hypertonus was unmistakable and persisted for about an hour.

There is little or no quantitative diminution in muscular power in cases of arteriosclerotic rigidity. Except in the later stages of the disease, the muscular force is commensurate with that of normal subjects of the same age and physique.

But while there is little or no paresis of the grosser movements of the larger muscle units, some subjective and objective defect in the execution of fine manipulative movements may exist, and these become slow and awkward in execution; such acts as fastening buttons, tying and untying string, piano-playing, typewriting and card dealing may be clumsy or even impossible. The handwriting often betrays this weakness, and becomes angular, interrupted or irregular, and in cases with distal rigidity there is a micrographia comparable with that seen in idiopathic paralysis agitans.

Rapidly alternating movements are performed slowly and irregularly. The disturbance is different from that seen in cerebellar disease, for in the latter there is always an exaggerated play of extraneous muscles; in alternate supination-pronation of the forearm, for instance, the elbow is rotated in wide circles by associated abduction movements of the upper arm. In arteriosclerotic rigidity there is much less defect of fixation, and associated movements in other parts of the limb do not occur to the same extent.

Bradykinesis, or slowness in the execution of voluntary movements, is one of the more characteristic signs. Thus, in the performance of the finger-nose tests the hand travels towards its goal with greater deliberation than normal. By ordinary clinical methods it is rare, however, to find any definite delay in the initiation or relaxation of a particular movement, except where cerebration is so retarded that the mental reaction time is prolonged. Foerster states that in the advanced stages there may be a very definite delay in the relaxation of a movement and the initiation of an antagonistic movement; the patient may show a little delay in reopening the closed fist after tightly clenching it. This observation has not tallied with my experience however.

Bradykinesis is not confined to those movements which one may regard as essentially voluntary. Slowness is also seen in acts which depend less on deliberate, volitional effort and which can be regarded more as "automatic." For example, if the patient is observed, without his knowledge, while he is eating or yawning, the movements are seen to be carried out with the same slowness.

Hall's accurate analysis [37] of bradykinesis has brought to light other points. He has confirmed, what has long been suspected on clinical grounds, that objective slowness of movement precedes the patient's knowledge of his disability. Patients with extreme bradykinesis show also a premature fatigue, which Hall terms "flagging." Although it is now agreed that bradykinesis is not necessarily dependent on rigidity, the two conditions are almost always combined. Moreover, an extreme degree of hypertonus increases the slowness of movement. On the other hand there is little or no relationship between muscular strength and bradykinesis.

The resemblance of the type of movement in arteriosclerotic rigidity to that in paralysis agitans is still further emphasized by the characteristic "poverty of movement" seen in each condition. This akinesis is most obvious when the patient is observed during the performance of some accustomed act, as reading or conversing; it is apparent that all expressional movement of the limbs and all play of gesture is reduced to the minimum, if not entirely absent. As Kinnier Wilson has pointed out in the case of the post-encephalitic syndrome, the patient never sits with the legs crossed or with the arms folded, does not fidget about in his seat, change his attitude or perform those numerous semi-purposeful movements of the normal individual. He sits erect and immobile and employs as few extraneous movements as possible. Differences between the arteriosclerotic and other types of Parkinsonism are those of degree only, being less marked in the former condition.

Reference has already been made to the fact that these patients show a weakness of walking which is out of proportion to the relative strength of the individual movements of the limbs. Thus, whilst the patient is supine each component action can be executed with almost full power, and yet his gait is slow, short-stepping and feeble in the extreme. In other words, there is an apparent dissociation between the strength of volitional and of automatic movements. This dissociation has been emphasized by Lhermitte, who points out that such delicate and essentially volitional acts as writing may be carried out with accuracy, whilst the more elementary activities of walking, phonation and swallowing are grossly impaired. The type of case referred to by Lhermitte is, of course, severer than those I am describing and would conform particularly to those of Type 2.

The influence of the emotions upon these more automatic movements is frequently striking; under the influence of sudden fear or during an instinctive response to danger, the gait may lose its feeble and short-stepping characters and approximate to the normal. This paradoxical kinesis, which is, of course, a commonplace feature of the post-encephalitic varieties, is less well recognized and less marked in the arteriosclerotic types of Parkinsonism. By accurate ergographic measurements of the strength of Parkinsonians under mental stimuli, Hall has shown that an increase of output of rather more than 10 per cent. is possible. He suggests that some of the descriptions given of paradoxical kinesis are probably exaggerated.

It is necessary at this stage to examine briefly the state of the various movements of minor order attendant upon or forming part of the main movement-complex. Following the example of continental writers it had become customary to speak of these movements as diminished or absent in Parkinsonian states, to ascribe their abolition to disorder of the corpus striatum, and to attribute to the striatum the functions of "centre" for the regulation of associated movements. Kinnier Wilson [102], however, has proved each of these three views to be incorrect, and based upon inaccurate and insufficient observation. Wilson's conclusions have been fully confirmed by Young [107] in a series of post-encephalitic cases. In the present series of cases of arteriosclerotic Parkinsonians I have been able to support Wilson's conclusions.

The vague and inadequate term "associated movement" includes many varieties of movement, and therefore following Wilson's classification I shall divide them as follows:—

(1) Movement synergias. (Wilson rightly employs the simple term "movement" when referring to this type, but for the sake of clarity the earlier nomenclature will be adopted here.)

(2) Movements of co-operation.

(3) "Associated" movements properly speaking (or imitative synkinesiæ.)

(4) Movements of reaction and defence.

Within the first group Wilson has included those component activities enumerated by Beevor, which by their simultaneous or successive contraction go to form a complete "movement" (or synergic unit); the contraction of the extensors of the wrist and of the biceps during a forceful handgrasp is one example of the many normal movement synergias. In no instance of arteriosclerotic Parkinsonism which I have examined have I found an abolition of any of these component activities. Although slowly carried out, each constituent movement was present and of normal amplitude.

By the expression "movements of co-operation" Wilson understood "movements which are auxiliary to each other, also 'voluntary' movements preceding or accompaning these as the case may be." Foerster spoke of them as "reaction movements." One example will suffice: When a patient seated on a chair is required to stand he first of all brings his feet underneath his trunk so as to place them under his centre of gravity. No loss of this movement has been noted in any case examined in my series, though the movement may be slower in initiation and execution than in the normal subject. Much attention has been paid to a loss of swinging of the arms during walking as a mark of striatal disorder. In many of the cases of arteriosclerotic Parkinsonism, however, I have not found any abolition of these arm movements. Indeed, in some cases the movements are carried out in an exaggerated fashion, but the movements usually differ from the normal in that no excursion takes place at the elbow-joints.

By the term "associated movements", or imitative synkinesis one understands those symmetrical and synchronous movements of corresponding opposite limbs. The two chief predisposing factors for the occurrence of such movement are (*a*) rapidity or delicacy of movement and (*b*) forced effort. Hence the synkinesiæ are apt to appear either with fine manipulation of the fingers, or with vigorous actions such as grasping. In executing the tests for dysdiadochokinesis, similar but mirror-opposite movements may often be seen in the contralateral limb. Synkinesiæ of this type may occur when the symptoms are bilateral and equal, as well as in those rarer cases in which the clinical manifestations are asymmetrical. In the latter case the synkinesiæ may appear in the less affected limb when the patient moves the more affected one—or vice versa. The imitation movements are feebler in force and amplitude than the primary movements; although "involuntary" in that they arise outside the subject's notice or volition, they are readily controlled when the attention is drawn to them.

Associated movements of this type are of course familiar in other pathological states, such as in pyramidal or cerebellar affections, in chorea, and in other states of Parkinsonism. Marie and Foix [65 indeed speak of a normal innate tendency towards imitation by one side of alternating movements of the other.

"Movements of reaction and defence" include those activities which result from definite noxious stimuli. Wilson has devised a series of chair-tilting tests to investigate the presence or absence of these movements. The manœuvres executed by the patient in the attempt to avoid a fall are noted. In not a few of the post-encephalitic Parkinsonians there is an apparent feebleness or absence of these movements. Thus Foerster remarked upon the indifference of such patients towards irritation from flies. Wilson was unable to find any constant absence of this phenomenon in post-encephalitic Parkinsonism, though there was a reduced response in some instances. In my series of cases of arteriosclerotic rigidity, in which these reactions were specifically investigated, no loss was encountered.

Analogous with these defence reactions are the so-called hyperalgesic reactions of Babinski and Jarkowski [45]. These authors found that nocuous stimuli applied to the distal part of an affected limb in cases of hemiplegia may give rise to a series of reactions of varying complexity. There may be an abrupt and generalized withdrawal of the stimulated member; at the same time the upper extremity may move down toward the area stimulated, or in other cases be brought up to the head. Facial distortions suggestive of pain and exclamations of protest may also be present. The whole phenomenon, which is really only a natural response to unpleasant stimuli, is exaggerated in cases of pyramidal disease so as to amount to a veritable "réflexe de défense encéphalitique." In cases of Parkinsonism, however, Jarkowski found these "affectivo-motor reactions" (as he later called them) reduced or abolished.

One of the most characteristic clinical features of this variety of Parkinsonism is catatonia (or catalepsy). A tendency towards the assumption of fixed postures has been noted by many writers on the subject of cerebral arteriosclerosis. Foerster drew particular attention to it in his original monograph and likened it to a monosegmental catalepsy. Lhermitte and others describe how patients allow their limbs to remain immobile in unnatural antigravity postures "as though they had forgotten them."

The presence of this catatonic tendency can be revealed by various devices. Thus if repeated passive movements of flexion and extension are made with the patient's upper limb and then support is abruptly withdrawn, the arm will remain for a time immobile. Again, if the patient's knee-joint is vigorously extended and flexed several times in succession and then suddenly released, the leg remains bent at the knee and ankle with the heel off the bed. Such an attitude may be maintained as long as half a minute. Sometimes if one raises one leg in order to investigate the tonus, the opposite leg is also raised and maintained for a moment or two in this unnatural pose. Foerster remarks that this catatonic tendency is especially marked if the attitude passively imposed is one of full degree, as for example full flexion of the elbow-joint, and that if the passive support is maintained for some little time before being released the catatonic tendency is usually pronounced.

In the severer degrees of arteriosclerotic Parkinsonism (as described under Types 2 and 3) catatonia is much more obvious and attitudes are maintained for longer periods. Moreover, the patient seems to adopt such postures as it were "spontaneously," without the intervention of passive manipulations (= the "spontaneous counterpull" of Kleist). Peculiar attitudes may be adopted: thus, one patient who belongs to Type 2 used to lie in bed with his left arm held stretched immobile immediately above his face, the limb lying at right angles to the long axis of the trunk, with the fingers fully extended and abducted.

This "spontaneous catatonia" must not be confused with the fixity of the patient in his characteristic flexor-attitude. Thus it would be incorrect to regard the bowed stance, the characteristic attitude of the upper limbs, or the "oreiller psychique" as evidences of a catatonic process. They are rather essential parts of the more universal "flexing factor" which Foerster holds responsible for the characteristic deformities and postures.

When the "flexing factor" preponderates, it may give rise to a phenomenon which opposes and appears to be the direct antithesis of a catatonic process. Thus, if the typical flexion-supination attitude of the patient's fore-arm is passively overcome by extending the elbow-joint, one of two phenomena may occur: (1) If the catatonic process is the more obvious, the limb will remain in extension for an undue length of time, frequently in an actual antigravity position; (2) on the other hand, if the catatonic tendency is outweighed by the greater development of the "flexing factor," the fore-arm will slowly and involuntarily flex until it has resumed again its typical resting attitude. In this way the "flexing factor" and the catatonic tendency may appear as clinically opposite phenomena.

Speech.—Some defect of speech is usually present in all cases of arteriosclerotic Parkinsonism, whatever the clinical variety. In general terms it is one of articulating and not of propositionizing; all varieties of disordered enunciation are encountered up to total anarthria.

In the milder cases—as in Type 1—the changes may be so slight as to escape the superficial observer. The voice is hushed, the pitch being unchanged, and there is a lack of cadence so that the rising and falling inflections are wanting. Later, some defect in the pronunciation of the consonants appears, the labials and dentals suffering more than sibilants and gutterals. The defect becomes more obvious when the patient speaks rapidly, or employs unusually long or difficult words. The more advanced stages are marked by a simple exaggeration of these traits; the speech, which is now definitely dysarthric, is enunciated in a characteristic monotonous fashion.

Patients whose clinical picture conforms to Type 2 show the additional traits of pseudo-bulbar palsy. There is a superadded blowing or nasal intonation testifying to palatal weakness, and in certain instances a kind of verbal festination whereby the rate of speaking accelerates towards the end of the sentence. The rate of the speech as a whole is usually increased and the final syllables may be clipped in an abrupt manner. Lastly, there is a characteristic "explosiveness" so that the patient embarks upon a phrase in a sudden and unexpected way. During bouts of involuntary laughter or crying these disturbances of speech become greatly exaggerated. Indeed, in some mild cases, the speech may be almost normal during the inter-paroxysmal periods. In the emotional spells the dysarthria is, of course, greatly increased, owing to the lack of co-operation of the lips in speaking, and a "braying" element appears, which results from a stridulent expiration of air through taut vocal cords.

In the last clinical group, where cerebellar manifestations co-exist, the speech may show other characteristics; it may resemble that of disseminated sclerosis in being staccato or scanning, and the nasal element may be very pronounced.

Comparable with the hypokinesis of the motor system, a poverty of speech appears at a relatively later stage in cases of arteriosclerotic Parkinsonism. In severe cases this may amount to an actual mutism, which is especially seen in the third clinical type, where severe dementia accompanies the Parkinsonian syndrome. It is never absolute; the patient sits taciturn and immobile; he utters no spontaneous sound, and replies rarely and only to frequently repeated questions of the simplest order. The replies may be unintelligible, being grossly dysarthric and hushed. Moreover, the patient employs the minimum of words in his replies, which tend to be monosyllabic or telegrammatic in form.

Among the more interesting of the disorders of speech sometimes associated with the Parkinsonian syndrome must be included palilalia. This defect, which comprises the involuntary repetition several times over of the terminal word or phrase, is especially apt to be seen in Types 2 and 3. As pointed out elsewhere [19], palilalia frequently co-exists with some degree of mutism, as though the patient were unwilling to embark upon the act of speech.

The palate and pharynx: disorders of chewing and swallowing.—Defects in the functions of chewing and swallowing are uncommon in the arteriosclerotic types of Parkinsonism, except in conjunction with the pseudo-bulbar syndrome, but in cases conforming to Type 2 several important phenomena may be encountered.

Dysphagia is by no means uncommon, but differs from that occurring in the progressive bulbar palsies in being less constant and less severe. The difficulty, moreover, varies in degree from day to day in the same patient. In both disorders there may be dysphagia for certain types of foodstuff only—fluid or solids; in both, semi-solids are swallowed with least discomfort.

Difficulty of mastication is a frequent complaint in the pseudo-bulbar varieties of Parkinsonism, and results partly from weakness of the masseters and partly from disordered mobility of the tongue.

Nystagmoid movements of the soft palate, pharynx and vocal cords are not infrequent. As a rule they cause no symptoms and are discovered accidentally in the course of routine examination. The movement may be confined to either the palate, pharynx or larynx, but as a rule all three structures participate in a rhythmic and synchronous movement. The involvement of the palate and pharynx is usually bilateral, while it is common for one vocal cord alone to be affected. The nystagmus occurs during rest and also during active movement of the part. The particular clinical group which is most apt to show these movements is Type 2, but they have also been seen in cases conforming to the fifth group.

The various reflex phenomena referable to the lips and tongue are of especial interest, but are apparently confined to the cases with "pseudo-bulbar" manifestations. These phenomena include the "buccal reflex" of Oppenheim (= "lip reflex" of Thomson) — the "hard-palate reflex" of Henneberg and the orbicularis reflex. They comprise the production of pouting, sucking and chewing movements ("Ansaugen") upon appropriate stimuli.

Reflexes.—The state of the superficial and deep reflexes varies a great deal, depending not only upon the clinical type of Parkinsonian syndrome, but also upon the presence of various extraneous factors. Thus, in addition to the co-existence of pyramidal affection or of cerebellar disease, one must take into consideration the influence of such all-important factors as age, decubitus, presence of contractures, arthritis deformans and muscular wasting. By reason of their frequency it will be advantageous to consider them at the outset.

Although all patients with arteriosclerotic Parkinsonism do not necessarily fall into the category of senescence, nevertheless advanced age commonly complicates the clinical picture. Its influence upon the state of the reflexes is proved, but the actual nature of such changes is a subject upon which no exact information is available. There is certainly, however, a frequent depression in the activity of the deep reflexes. The effect of old age upon the pupillary responses, and upon the rectal, vesical and genital reflexes will not be considered. A diminution and later abolition of the abdominal response is, of course, well known. Absence of the Achilles jerk with conservation of the knee and arm reflexes, is by no means an uncommon finding in healthy old age. It is doubtful whether a Babinski type of response is ever seen in cases of normal senescence, although occasionally said to occur.

In bedridden patients with cerebral arteriosclerosis the tendon reflexes become further altered by the development of contractures. A permanent attitude of flexion results and it may be quite impossible to elicit patellar or ankle jerks. Arthritic changes, particularly in the upper extremity, produce a similar difficulty in testing the reflexes.

In the few cases in which the influence of advanced age, of contractures and joint changes is non-existent, the tendon-jerks are active, but the typical motor response is slow and gradual in attaining its summit and the return to the resting posture is prolonged. Clonic responses are not usually obtained. The abdominal responses may be elicited, but they tire readily, so that after three or four successive stimuli no contraction results.

In uncomplicated cases the plantar responses are of the flexor type. I have not succeeded in changing the character of the reflex by altering the posture of the head or neck (Walshe [101]). Rosenfeld's method [83] of changing the character of the plantar response by means of hyoscine has not been tried in this series.

In cases in which a pyramidal affection exists in association with the pallidal disease, there is a change in the character of the tendon-jerks. The delayed contraction and gradual relaxation are less noticeable and a clonic element is superimposed. This latter may only be revealed by graphic methods. The superficial abdominal responses are abolished and the plantar reflexes are extensor in type. Sometimes, when the pyramidal disorder is presumably slight in degree, the plantar response may be extensor in type when the stimulus is applied to the outer side of the sole, and flexor when the inner side is stimulated.

Another type of variability in the plantar response has been noted in cerebral arteriosclerosis by Buzzard and Barnes. In their patient plantar stimulation evoked an extensor response when the leg was extended, but the reflex changed to the flexor type when the limb was flexed. They applied the term "pyramidal equilibrium" to this phenomenon.

Hyperkinetic manifestations.—Besides the hypokinetic-hypertonic manifestations which, as we have seen, form the background of this syndrome, other symptoms of a hyperkinetic nature are occasionally encountered. These are of the utmost diversity and vary in complexity from involuntary movements of a simple repetitive nature to complicated psychomotor activities of an almost purposeful type. Thus at one pole we have simple tremor or choreo-athetosis representing a hyperkinesis which is purely involuntary and almost beyond the control of volition; at the other extreme lie the parakinesias, expressive movements, motor stereotypy; the echopraxic and palipraxic phenomena, movements of sucking, tasting and smacking of lips ("Ansaugen"), forced grasping and groping, clutching movements initiated by visual stimuli, akathisia, movements of rubbing and stroking and so forth.

Many of these activities have been studied by the German school, particularly by Kleist [47] and [48].

Hyperkinetic manifestations are on the whole uncommon in arteriosclerotic Parkinsonian states; the absence of tremor is indeed a point of differential diagnostic importance. When the more complex psychomotor signs occur there is usually a severe co-existing degree of intellectual enfeeblement. This does not hold true for the simpler types of involuntary movement of tremor or chorea. In diffuse cerebrovascular disease when akinetic phenomena are prominent there are as a rule few, if any, evidences of hyperkinesis, but exceptions occur. Thus in the second case of Stief, Kleist's Case 1, and Freund and Rotter's first patient, tremor of hands, head or jaw, was associated with arteriosclerotic Parkinsonism. Sicard and Paraf's patient exhibited choreo-athetotic movements; movements of grasping and groping ("Zwangs- und Nachgreifen, optisches Kurzschlusshalten, Festhalten") were described in association with a hypokinetic-hypertonic syndrome by Schuster and Pinéas and by Kleist (Cases 1 and 7, of 1927). The behaviour of these patients closely resembled that of some of the patients with frontal tumour described by Adie and Critchley [1].

Involuntary movements of the palate, pharynx and vocal cords were seen in the cases recorded by Crouzon, Dereux and Kensinger, Signorelli, Lhermitte and Cuel, and Lhermitte and McAlpine. Lastly, among the miscellaneous involuntary movements of complicated order may be mentioned Stief's fourth case, the first and sixth cases of Kleist's (1922 paper) and Noethe's patient. One patient in my series exhibited many psychomotor activities in the form of plucking at his nightdress, fingering the coat and stethoscope of the examiner, touching, rubbing and stroking.

Kleist's first patient (1922 and 1927 papers) showed explosive mimic movements and sucking, as well as forced grasping. In the right hand there were, in addition, movements of pill-rolling, rubbing, grasping and touching. In Case 6, parakinesis and palipraxia were present.

Noethe's patient showed with the left hand movements of striking the head, clutching the hair, grasping the genitalia, shaking hands, pulling at the bedclothes, forced grasping and echopraxia.

Stief's fourth patient performed complicated movements of packing objects in bed; and at a later stage, when grossly demented, she would slowly transfer to the mouth any object placed in the hand.

The psychological aspect.—Psychical changes are both frequent and important in the arteriosclerotic varieties of Parkinsonism. In some instances mental change appears very early and may indeed antedate the appearance of physical disorder; in such cases the psychical manifestations tend to occupy the foreground of the picture. Other cases show little or no mental change until the terminal phase of the disease. Cases which I have relegated to the second type are especially prone to be characterized by psychical defect, but none of the other groups is exempt from similar change.

In the milder cases the onset of the intellectual impairment may for a long time escape notice, and such changes as may be present are often ascribed to senility. The severer grades are usually regarded as examples of senile or arteriosclerotic dementia.

The main psychological features indicate a gradual process of cerebral dissolution; in short, they comprise a global dementia, which may be variable in degree, together with some change in affectivity. The earliest signs usually appear insidiously, although an acute onset following a stroke or an illness does not argue against the diagnosis. Among the early symptoms is a falling off in the patient's intellectual capacity; he may still be able to cope with the ordinary routine of his occupation, but any fresh or unusual demand upon his intellect fails to evoke the normal ready response. This failure of mental elasticity causes the patient to feel jaded and harassed when faced with problems lying outside his usual experience. An anxiety state not infrequently results and many patients seek advice and are treated as "neurasthenic." These delicate criteria of dissolution may not be apparent in the less cultivated type of individual; in the words of Hughlings Jackson [40], "much depends upon the type of brain he had before his illness."

Later, the patient may show an unwillingness to cope with novel situations or to embark upon unwonted enterprises; he tends to "fall back upon himself" and to be inattentive to external concepts and stimuli. He then appears forgetful of the trivial events of the day, and complains of defective memory. There is no failure, however, in recalling the remote past, and in later stages we find the "anecdotage" and conservatisms of senility.

Parallel with this intellectual impairment, a gradual limitation of the field of interest is often apparent. The patient becomes self-centred and frequently selfish, and the troubles of his friends and relatives leave him singularly unmoved. But within this narrowed sphere there is an instability in the emotional tone and a corresponding lack of expression-control. Tears and laughter are readily evoked, frequently without corresponding affective concomitants.

Variability in the degree of mental change is often striking. Many of these patients have periods of clarity which alternate with periods of clouded consciousness. Under treatment, or after admission to hospital, the symptoms tend to improve in a striking way. Hughlings Jackson [40], speaking of the mental symptoms of softening of the brain, distinguishes carefully between the active or positive manifestations due to the removal of inhibitory control and the negative ones which result from the loss of substance of part of the functioning brain. The latter type of change, he states, may slowly develop weeks, or even months, after an acute vascular crisis. A consideration of the individual symptoms as occurring in a severe or long-standing case may be shortly considered.

Disturbance of the centripetal functions is present in all severe cases, so that the patient's perception is defective and delayed ; in severe cases there is no link whatever between the patient and his environment. Illusions, or perverted comprehension of precepts, are not common. Hallucinations may occur, but are rarely systematized or vivid.

Ideation and the power of abstract thinking is, of course, completely lost in the severest stages, but an assessment of the patient's ability is much impaired by difficulties in co-operation ; defects in self-expression and the delayed perception may give rise to an erroneous and inadequate idea as to the state of mentation.

Association processes are characteristically retarded in the arteriosclerotic, and the number of available concepts is reduced. Processes of calculation and of expressing a coherent opinion upon an abstract subject are impossible. The patient passes with difficulty from one idea to another, and the first concept, once grasped, tends to occupy consciousness to the exclusion of fresh incoming ideas (ideational inertia: perseveration). A similar lack of mental agility is also seen in some cases of post-encephalitic Parkinsonism, and to this Claude has applied the term bradyphrenia, or "mental viscosity." Delusions or erroneous ideation may occur and take many bizarre forms. Among the more usual varieties are nihilistic, hypochondriacal, and micromanic delusions.

Disorders of memory are among the earliest and most characteristic of the psychical aberrations. A defective impressibility is a most obvious feature, so that the memory for recent events always suffers much more than that of the distant past. Sometimes the memory of familiar surroundings may be so impaired that the patient loses himself in his own house and is unable to find his way about the neighbourhood. Confabulation is not a feature of this type of disorder. Bleuler has called attention to the presence in the senile of cryptomnesia, whereby the patient, having at first rejected a new idea, finally assimilates it and then publishes it and passes it on as original—perhaps even to the very person whence it was obtained. Disorientation as to time, place and person is almost constant.

Clouding of consciousness, either permanent or episodic, may occur in the late phases. At night-time there is frequently some degree of delirious excitement which contrasts strangely with the patient's diurnal impassivity.

Changes in affectivity are frequent; in the earlier stages, particularly in cases belonging to Type 3, there is a marked emotional incontinence with spontaneous weeping and laughter. It is doubtful, however, whether these emotional displays are in any way a true representation of the actual feeling tone. Certainly in the later stages there appears to exist an apathy. When there is a constant departure from the normal feeling tone, the usual affect is one of depression rather than of exaltation.

The power of attention suffers in most instances—so that there is a difficulty in fixing the patient's mind on a particular theme. Once the attention is aroused, however, a marked prolongation occurs, and the mind is with difficulty directed towards a fresh idea.

Suggestibility is usually defective; in some cases a negativistic trend is present, so that suggestion evokes a contrary response. Alterations in personality, in the nature of transformations, are not usual in this type of patient.

The diagnosis from other senile and presenile psychoses is not readily made on purely psychiatric grounds. Although there is usually little or no difficulty in distinguishing a pure case of senile dementia from one of arteriosclerotic dementia, nevertheless in cases of arteriosclerotic Parkinsonism the mental symptoms may resemble either type. Thus one patient may show mental symptoms conforming to the arteriopathic order, and another to those of the senile type. Characteristic hypertonic-hypokinetic signs usually differentiate these cases from the other degenerative psychoses, such as Pick's disease, Alzheimer's disease and presbyophrenia. Furthermore, the pathological restlessness seen in the early stages of Pick's disease and presbyophrenia rarely occurs in the arteriosclerotic Parkinsonian.

Onset and course.—In the majority of cases the onset of the Parkinsonism is insidious and the progress steady and gradual. There is no history obtainable of any preliminary stroke. The course of the malady therefore resembles that of the idiopathic variety, but differs in being more rapid.

A smaller group of patients with arteriosclerotic Parkinsonism date their symptoms from an abrupt onset, which is usually of the nature of a mild apoplectic stroke. The progress of the disease is then characterized by a series of mild seizures, mostly of temporary character, but followed by a slight though definite increase in the basic disability. Marie, Ferrand and others have stressed this latter type of progression and have associated it with the pathological conception of progressive lacunar disintegration. Each attack is transient and is not attended by loss of consciousness; the paralysis is usually slight in degree and frequently monoplegic in distribution. Ferrand and his co-workers were mainly interested in the phenomenology of these acute exacerbations; it is the resultant chronic condition which we are at present considering under the category of arteriosclerotic Parkinsonism.

There is a third and still rarer mode of onset in these hypokinetic-hypertonic syndromes of arteriosclerotic origin; thus a unilateral Parkinsonism may follow a stroke. In such cases a hemiplegic distribution of rigidity, with little or no paralysis, no tremor, and no reflex evidence of pyramidal disease constitutes the clinical picture. Amongst cases of this type, recorded in the literature, are those of Bechterew [5] (who employed the term "hemitonia apoplectica"), Pfeiffer [77], Loewy, Mingazzini (whose case was peculiar, in that the clinical signs were on the same side as the pathological lesion), and Boettiger [6], who spoke of "hemi-hypertonia apoplectica" or "extracapsular hemiplegia."

The termination of the malady is always fatal, though the exact mode of death is variable. In some cases the patient becomes bed-ridden and incontinent with the legs completely paralysed in extreme flexion; difficulty in swallowing appears and he can no longer feed himself; articulatory defects render the patient unintelligible; consciousness is clouded and intellectual enfeeblement is profound. The ultimate phase is that of the "démence paraplégique" described by Deny and Lhermitte. Death usually results from broncho-pneumonia.

Such is the characteristic termination in the decrescent or senile type of arteriopath. In younger patients, in whom there is usually an increased blood-pressure, death may be sudden. In such large vascular lesions of a focal nature are common and the patient succumbs to a severe cerebral hæmorrhage or softening.

Differential Diagnosis.

The diagnosis of cerebral arteriosclerosis is usually easy and cases of arteriosclerotic Parkinsonism are often recognized at sight. The differences between arteriosclerotic Parkinsonism and other syndromes of cerebral vascular disease are those of degree rather than of quality. As previously emphasized, the pseudo-bulbar, the lacunaire and the arteriosclerotic dement frequently show in some degree the features of Parkinsonism, and a too sweeping classification of cerebral arteriosclerosis is neither possible nor desirable. Most difficulty lies in the differentiation from idiopathic paralysis agitans. As previously stated, it is doubtful to what extent the two conditions are actually separable; cases exist which are difficult to place in their proper grouping and these probably represent transition types. Usually, however, the two conditions are clinically distinguishable.

The onset of the symptoms may be different in the two cases. In the idiopathic variety the disease starts insidiously; a similar mode of onset may occur in the arteriosclerotic, but in a certain number the symptoms date from an acute apoplectiform attack. Secondly, the course may vary in the two diseases. In true paralysis agitans the advance is slow but steady. In arteriosclerotic Parkinsonism the advance is usually more rapid, or the disability increases by a series of step-like progressions, each exacerbation corresponding to a mild seizure.

The clinical manifestations are not quite identical. Thus a monoplegic or unilateral distribution of symptoms is rare in the arteriopathic varieties though common in paralysis agitans. In both types the facial expression is fixed, but in most of the vascular cases there is little or no smoothing out of the wrinkles and less facial greasiness. Typical pill-rolling tremor is almost always absent from the arteriopathic cases, though a "senile" type of tremor may be seen in the head, jaw or hands of the decrescent cases. The character of the rigidity is very similar in the two conditions, but the "cogwheel" phenomenon is rarely obtained in the arteriopath. Some authorities have been impressed by a greater firmness of the muscles on palpation in arteriosclerosis, but my experience does not altogether support this view, except in some of the older and bedridden patients. Jakob and others believe the muscles and tendons stand out more prominently in the symptomatic types. In the late stages the arteriopath probably shows more contracture and joint change than the true Parkinsonian. One of the most important points of differentiation is catatonia, which is rarely seen in true paralysis agitans. Severe symptoms referable to the bulbar mechanisms (dysphagia, dysarthria, sialorrhœa) suggest an arteriosclerotic basis to the malady. In most cases of arteriosclerotic

Parkinsonism the gait differs in certain minor particulars from that of true paralysis agitans. For example, the arteriopath almost always swings his arms, though in a stiff and automaton-like manner, and festination and propulsion are less obvious.

Psychical changes are important in differentiating the two types. Mental enfeeblement is an uncommon symptom of paralysis agitans and never appears until the late stages. In the arteriopath mental changes are, of course, very common; they are severer in degree and earlier in their appearance. The presence of emotional instability, with facile laughter and tears, is strongly suggestive of a vascular basis. Incontinence of urine and fæces rarely occurs in genuine paralysis agitans; indeed Gowers stated he had never met this symptom, while defective sphincter control is frequent in the arteriosclerotic forms.

In distinguishing between the two types, evidences of peripheral or retinal arteriosclerosis must be sought for. A negative finding does not, of course, exclude the cases of senile rigidity nor altogether the arteriosclerotic types; on the other hand, the demonstration of definite arterial disease in the periphery is suggestive of a vascular origin.

The presence of other focal manifestations (cerebellar or pyramidal signs, aphasia or apraxia, palilalia, choreiform or other involuntary movements not seen in paralysis agitans) suggests an arterial origin.

Lastly, the age factor is often helpful. Idiopathic paralysis agitans is a "disease of the degenerative period of life, but not of extreme senility" (Gowers). In the majority of cases, the symptoms arise in the sixth decade; the average age of onset was 52 in Gowers' series, while it was rare for symptoms to appear after the age of 65. In the arteriopathic cases the age of onset varies according to the type of arterial disease; many of the cases associated with hypertension and arterial changes of moderate degree start at a comparatively early age; many of them become affected between the ages of 40 and 50. With the cases of decrescent vascular degeneration, however, in which the blood-pressure is often low, the age incidence is much later and as a rule occurs at a later stage than paralysis agitans. An onset after the age of 65 is not uncommon in such cases, many of which belong to the clinical sub-type of senile rigidity. In short, symptoms of Parkinsonism commencing either early or very late (before 45 or after 70) are more likely to belong to the arteriosclerotic category.

Apart from other syndromes of cerebro-vascular disease there are but few disorders which bear any resemblance to arteriosclerotic Parkinsonism. Cases of post-encephalitic Parkinsonism occurring in middle or advanced life may cause confusion, but can be distinguished by the presence of ocular signs, by a greater degree of greasiness of the skin, and by different psychological concomitants, quite apart from a history of acute encephalitis.

Cases of mesencephalitis syphilitica are distinguished by the presence of additional characteristic signs, such as pupillary alterations, hypalgesic areas, defective postural sensibility and abolition of the tendon reflexes. A history of venereal infection and positive serological tests confirm the diagnosis. In these cases, too, the evidence of a peripheral arteriosclerosis may be wanting.

Reference has already been made to those states of pseudo-Parkinsonism which may accompany ankylosing spondylitis or arthritis deformans. Except in cases where true paralysis agitans co-exists with severe joint changes, there should be no real difficulty in distinguishing them.

Some difficulty may be anticipated in separating the cerebello-pallidal type of arteriosclerotic Parkinsonism from other cerebellar syndromes of the aged, in particular olivo-ponto-cerebellar atrophy (Dejerine and Thomas), olivo-rubro-cerebellar atrophy (Lejonne and Lhermitte), delayed cortical atrophy (Marie, Foix, Alajouanine, etc.) and the various transitional forms (Ley). These disorders are, as far as we know at present, associated with a senile process and bear no direct ætiological relationship to cerebro-vascular disease; hence the presence of peripheral or retinal arteriosclerosis will suggest a cerebello-pallidal syndrome. A sudden or apoplectiform onset, or a step-like progression in a downhill direction, suggests cerebral arteriosclerosis. The co-existence of other focal brain manifestations is not to be expected in the senile cerebellar syndromes. The pressure of well-defined extrapyramidal signs (bradykinesis, mask-like face) are points in favour of cerebral arteriosclerosis. Lastly, the true senile cerebellar syndromes are not, as a rule, associated with mental change. In the majority of cases the state of the muscle tonus is a valuable diagnostic point, for a normal or diminished tone occurs in the senile atrophies, though in the terminal phase rigidity may be present (Ley [51]).

Differentiation has also to be made, as Lhermitte has shown, from those cases of senile paraplegia due to purely muscular changes. The main distinguishing feature of senile myosclerosis is a high-grade generalized muscular wasting with myoidema; the course is slower and there is a relatively long interval between the affection of the legs and implication of the trunk, neck and arms. Frequently passive manipulations of the affected limbs are impossible, and attempts at so doing elicit pain. In addition, there are two symptoms of arteriosclerotic rigidity which are rare in senile myosclerosis, namely catatonia and mental change.

CHAPTER IV.—MORBID PHYSIOLOGY.

The nature of "arteriosclerotic rigidity."—A certain amount of doubt exists as to whether a single pathogenic agent is responsible for the various forms of rigidity met in arteriosclerosis. In a large proportion of the cases the hypertonus cannot be due to pyramidal disease, and even when this is present it obviously cannot account for the whole of the rigidity.

The "plastic" character of the hypertonus, the bradykinesis, the poverty of spontaneous movement, the attitude, facies, stance and gait of the patient suggest a close analogy with the amyostatic syndrome of extrapyramidal disease. It has been customary, therefore, to attribute these symptoms to disorder of the corpus striatum, and of the pallidum in particular. Hence the syndrome of arteriosclerotic rigidity has been associated with the hypertonus of idiopathic paralysis agitans.

Before accepting such an opinion unconditionally, it is advisable to broaden our observation of the clinical phenomena and interpretations thereof rather than to focus the whole attention upon the pallidum. Closer examination of the character of the rigidity and the factors influencing its intensity, coupled with an appreciation of the psychological aspect of the patient, will reveal other features which do not form an essential part of the true Parkinsonian syndrome.

In the first place, the hypertonus appears to be more under the influence of psychological factors in the arteriopath than in the true Parkinsonian. Thus, the degree of rigidity varies with the amount of force used in passive manipulation. Again, by distracting the patient's attention, the degree of rigidity is lessened, although not removed. In some patients these factors are so obvious that the rigidity may lightly be attributed to an inability to relax. But when by appropriate measures the whole of the psychological factor is eliminated there is still an obvious residuum of increased tonus. Foerster has shown that this rigidity is demonstrable even during sleep. On the other hand, by employing those devices which remove the reflex component of the rigidity (i.e., by novocain de-afferentation) an obvious reduction occurs in the degree of hypertonus.

Nor is it wise or even justifiable to disregard entirely the obvious "difficulty in relaxing" which these arteriopathic patients show. This inability to relax, so constant and so potent a factor in this disorder, is seen in few other clinical conditions with the same frequency or intensity. It may well be compared with the rigidity occurring in cases of dementia præcox, in which the rigidity is the physical reflection of the mental state of negativism. A similar state of mental resistance does not occur in cerebral arteriosclerosis to the same extent, although it cannot be said to be entirely negligible. Kleist indeed regards a state of psychomotor negativism as all-important in the production of counter-pull. Psychological factors of even greater prominence in the cerebral arteriopath are a defective accessibility and an impaired appreciation of the impressions received. This intellectual defect is mirrored in the physical condition by an impaired ability to grasp the wishes of the examiner, or to assist him by the relaxation of the muscles. Passive manipulation of the extremity, therefore, produces an automatic and almost "reflex" tightening of the muscles as if in opposition.

Inability to pass readily from one concept to another shows itself by a failure to grasp quickly what is required. This ideational inertia is reflected in the physical state by a tendency towards motor perseveration, so that successive commands may evoke identical responses. To some extent the hypertonus may be the expression of a perseveration whereby rapidly alternating passive movements, as of flexion and extension of a limb, tend to be resisted. Two chief clinical phenomena illustrate this point: first, if the limb is rapidly moved in a direction of alternate extension and flexion, and then abruptly released, the patient may of his own accord continue to make feeble flexion-extension movements simulating those carried out by the physician. These palipraxic "after-movements" persist for only a short time. The second illustration lies in the assumption of catatonic postures, a feature which will be discussed later

When evaluating the various factors in arteriosclerotic rigidity, it is necessary also to investigate the peripheral mechanisms. Changes of a senile or trophic character in the joints, tendons, or muscles are frequent and important factors. The presence of a deforming arthritis in the joints of the limbs is of itself apt to produce, by a process of partial ankylosis, a spurious increase of tone in the affected extremity. This pseudo-rigidity, combined as it often is with a poverty of spontaneous movement and slowness in execution, may simulate the hypertonic-hypokinetic syndrome of paralysis agitans Indeed, through the writings of Brissaud, Delachet, Sicard [87], Lhermitte, Steck [91] and others, the French have been long familiar with the clinical conception of a "syndrome parkinsonienne à forme arthritique" or the "maladie de Charcot-Landré-Beauvais." The stance and bowed attitude of the Parkinsonian, and even the impassive face, is closely simulated in the aged by conditions of cervico-dorsal kyphosis, with ankylosis of the occipito-atlanto-axis articulations, a clinical commonplace in institutions for the aged.

Contractures appear early in senile and arteriosclerotic rigidity, and advance apace as soon as the patient becomes bedridden. Typical deformities appear in the hands; the flexed attitude of the legs becomes extreme, so that passive extension is quite impossible, and the tendon reflexes become difficult to elicit.

The causation of early contracture in arteriosclerosis is obscure, but is usually attributed to implication of the meninges or ventricles (Gaussel [33]. In cases of multiple vascular lesions, however, a type of contracture may appear which is spoken of as "pseudo-précoce," that is to say, a slight and transient stroke is followed almost immediately by the development of contractures of a "late" type. Bard [4] has suggested that in such cases the contracture is really an expression of diffuse or multiple lesions; the stroke which appears to be responsible is not the sole agent, for other and slighter seizures have occurred previously; hence the contracture is a "late" one, if dated from these original and often negligible attacks. Such an hypothesis may be applicable to the severe and early development of contracture in cases of arteriosclerotic Parkinsonism.

Other severer and more permanent shortening processes may occur in the tendons around the joints. These "retractures," as they may be called, do not disappear under even the deepest anæsthesia, and after death tenotomies may be necessary to straighten the limbs.

Fibrotic changes in the muscles themselves still further augment the rigidity. Lhermitte, both alone [52 and 55], and in collaboration with Lejonne [50], has described under the title "Myosclérite rétractile progressive," or "Myopathie sénile et primitive," the clinical and pathological aspects of this complicating factor which develops with such rapidity in the bedridden patient. The aged are particularly susceptible. Changes of this character located within the muscles contribute to the feeling of hardness on palpation. Moreover, the intrinsic changes in the muscle assist in the so-called "formgebenden" rigidity whereby tendons and muscles stand out prominently in contour. There is always a great diminution in the bulk of the muscle, and the mechanical excitability is increased. The muscles are tender on palpation and attempts at passive manipulation are painful. No changes occur in the reflexes sensibility is intact; there is a slight diminution in electrical excitability but no reaction of degeneration. It is remarkable that so important a clinical observation as the existence of a senile form of myosclerosis should escape comment, although the subject has been reopened in more recent years by Fumet [31].

In cases of partial or intermittent ischæmia of the extremities from disease of the peripheral vessels, there also occurs rigidity or cramp of a temporary nature. Thus, in cases of intermittent claudication the affected muscles go into a state of spasm coinciding with the period of least arterial supply. To a lesser degree the same phenomenon may be seen in Raynaud's disease and in acroparæsthesia; similar states of peripheral arterial disease are present in many of the cerebral arteriopaths, and it is highly probable that spasticity of peripheral origin contributes to the total rigidity. Such a conception would explain in part the marked influence of cold in increasing the rigidity.

Finally, account must be taken of the possible existence of changes in the peripheral nerves. Although comparatively little attention has been paid to the subject, the evidence of Schlesinger [85], Franceschi [28] and others, demonstrates that a peripheral neuritis of an arteriosclerotic basis does occur. In certain instances of diffuse cerebro-vascular disease, therefore, it is possible that changes in the peripheral nerves contribute to the hypokinesis, as well as to the formation of contractures and intramuscular fibrosis.

When rigidity of a pyramidal order is demonstrable there will appear characteristic tendon responses, knee and ankle clonus, and Babinski's phenomena. A true defence reflex may be obtainable. It is to be noted, however, that all the reflex signs of pyramidal disease cannot always be demonstrated, and sometimes ankle and knee clonus may be obtained whilst the plantar reflexes remain flexor. Conversely, extensor plantar responses may exist without any clonus being obtainable.

Buzzard and Barnes have described under the term "pyramidal equilibrium" a condition in which the functional integrity of the pyramidal tract seems to waver in the balance. It may be advisable to recall at this point the work of Walshe [100], and also Marinesco and Nicolesco [67], who found, after the injection of hyoscine in cases of idiopathic paralysis agitans, that the plantar responses temporarily became extensor in type. Walshe discussed the possibility of a clinically latent disturbance of pyramidal function being present in apparently pure examples of paralysis agitans.

We are led, therefore, to a wider conception of the pathogeny of the rigidity syndromes in cerebral arteriosclerosis. It is no longer justifiable to attribute the hypertonus wholly to pallidal disease, in fact, it seems that lesions at all levels of the central nervous system, and even of some extraneural mechanisms, may contribute. And we cannot disregard the psychological factors, as defective co-operation and even active resistance. The pyramidal motor system certainly contributes to the rigidity in a proportion of cases. Lastly, structural changes in the joints, tendons, muscles, and peripheral blood-vessels may play an important rôle.

Reference has already been made to the extreme difficulty with which voluntary resistance and failure to relax are overcome in the arteriopath. In some of the more demented patients it is possible that this factor is insurmountable. Wilson has suggested that even in [illegible] whom an apparently complete relaxation has been effected [illegible]ins an element of psychomotor resistance over which the [illegible]o voluntary control. In such cases one is struck by a [illegible]ith the phenomena of apraxia, and the possibility of an unconscious apraxic type of rigidity must be borne in mind.

The nature of catatonia.—The frequency with which attitudes passively imposed are maintained by the patient is a striking feature of the cerebral arteriopath. This manifestation is especially common in all Parkinsonian syndromes associated with arteriosclerosis, and occurs in all the types described.

Much confusion has arisen with regard to terminology. The word "catatonia" has been employed throughout this paper to describe this phenomenon, in spite of possible confusion with that type of dementia præcox named "katatonia" by Kuhlbaum. Psychiatrists apply the term "catatonia" in a rather vague manner to several discrete neurological phenomena bearing little or no relationship to each other. Thus "catatonia major" is applied to the spontaneous assumption of statuesque poses, whereas "catatonia minor" is used to include verbigeration, stereotypy and negativism. "Flexibilitas cerea" is a term frequently used for the clinical phenomenon in question. Amongst continental authors the word "Katalepsie" (or "catalepsie") is in favour, but its use in this country in a different sense and the possibility of confusion with cataplexy argue against its adoption. "Contraktionsnachdauer" and "Haltungsverharen" are also at times used synonymously with Katalepsie.

In organic neurology catatonia is usually intimately associated with rigidity, the nature of which is pallidal rather than pyramidal.

The first question which arises in a discussion of the nature of catatonia concerns its relationship with rigidity. In cerebral arteriosclerosis, catatonia is essentially bound up with the phenomena of rigidity, and is not seen in patients with a normal muscle tonus. In various psychoses the association is less definite; in dementia præcox a rigidity may be demonstrable, but of an entirely different nature; psychical factors in all probability constitute the sole pathogenic agency and it is not necessary to postulate structural changes in the motor system. Moreover, in the psychoses catatonia is quite often present in the absence of rigidity.

Demole claims to have produced catatonia in cats and rabbits experimentally by injecting solutions of sodium or potassium chloride which produced destructive lesions in the basal ganglia, and particularly in the thalamus."

Wilson [103], however, has produced evidence to show that catatonia may occur as a concomitant of a pyramidal type of spasticity. His patient was an elderly man who was admitted to hospital in a semi-conscious state twenty-four hours after a stroke. There was a right-sided hemiplegia with rigidity, and some degree of aphasia. The deep reflexes were increased on the right side; the plantars were both in reduced flexion, and a crossed plantar response was obtained from the right sole. When the patient was placed upon his left side, the right lower extremity was passively abducted at the hip and flexed to a right angle at the knee. This awkward position was maintained for three minutes. Two Jacksonian fits commencing in the right arm appeared on the following day. The diagnosis of cortical (submeningeal) hæmorrhage over the left ponto-parietal region was made and corroborated at autopsy.

There is but one neurological condition described, namely, cerebellar disease, where catatonia may occur in association with states of diminished muscle tonus. Although, contrary to general experience, Babinski [3] has emphasized a "catalepsie cérébelleuse" in the human subject, while Luciani, Thomas, Greggio, Borgherini and Gallerani have observed the same after experimental ablation of part or whole of the cerebellum in animals.

The ordinary cases of pallidal rigidity (exemplified by paralysis agitans, post-encephalitic Parkinsonism, progressive lenticular degeneration) show an increase in the degree of plastic (or postural) tonus. Many of them, as pointed out by Foerster, tend to fix the limb whatever muscle length is passively imposed (fixation-rigidity:

Adaptionsspannung). True catatonia, however, is not typically met with; as Wilson wrote [102], "catatonic phenomena have no place in the syndrome."

Catatonia, therefore, is a symptom which can appear in association with pyramidal or extrapyramidal types of rigidity, but which is independent thereof. It may occur as a psychotic manifestation unassociated with motor disability, although accompanied by a psychical type of rigidity. Lhermitte concludes that catatonia is the result as much of a suggestibility due to psychical disintegration as to a disorder of innervation resulting from pallidal destruction. Steck [91] regards catatonia as a link connecting organic with functional phenomena.

We may, therefore, speak of "motor" and "psychical" components of catatonia. Within the motor complex are included all the hypokinetic-hypertonic manifestations of pallidal disease together with a fixation-rigidity. Pallidal disease of itself is unassociated with catatonia, unless the psychical component is also present.

Marinesco [66] has suggested that the cerebellum might participate in the mechanism of catalepsy (catatonia) associated with Parkinsonism, and demonstrated lesions in the dentate and roof nuclei in fatal cases of acute epidemic encephalitis in which catalepsy had been a prominent symptom during life.

Defective mentation is an all-important agent in the production of catatonia, just as in arteriosclerotic rigidity. A disordered power of perception, lack of attention and retarded cerebration together contribute towards a definite ideational inertia. The patient is unable to grasp successive concepts if following too close on one another; if the suggestion takes the form of a command there will result a perseverated motor response. If, on the other hand, it takes the form of an attitude passively imposed upon a limb-segment, the posture tends to be maintained against gravity for an undue length of time. Either of two views may be hazarded to explain this: on the one hand, the patient may be unaware of the attitude of his limb in space, the proprioceptive impulses failing to reach consciousness on account of the dementia. In other words, the patient becomes for a while oblivious of the existence of his limb. Or, on the other hand, the patient's sensorium may be replete with the suggestion of the new attitude passively imposed, to the exclusion of fresh ideas. It is not until this initial suggestion wanes or becomes replaced by the painful impulses from the tiring muscles that the catatonic attitude is interrupted.

CHAPTER V.—PATHOLOGY.

Although the scope of this communication is essentially clinical, it is impossible to discuss arteriosclerotic Parkinsonism without reference to its pathology. Hence, the anatomical data available in the literature have been examined with a view to determining the extent to which a pure pathological picture is forthcoming. The subject will be discussed along general pathological lines, and then the correlation of structural with functional change will be examined.

General Pathological Considerations.

The nature of the pathological process underlying the arteriosclerotic types of Parkinsonism is by no means uniform. All manner of regressive changes may be encountered, primary as well as secondary. The pathological picture will vary, moreover, according to the degree of abruptness of the ischæmic process.

Detailed description of the pathology would be far beyond the scope of this paper. It will suffice to mention quite briefly the more important morbid processes which may be encountered. For the sake of convenience one may regard the cerebral changes under three heads: (1) gross vascular lesions; (2) minute vascular lesions; and (3) changes consequent upon old age. It is obvious that any combination of these may occur.

The gross vascular changes include macroscopic areas of hæmorrhage or softening, lacunes of cerebral disintegration, and the "état criblé." They also include alterations in the cerebral coverings; thus the dura may become thick and hardened, small areas of calcification are not uncommon, and actual ossification may be present. Changes in the leptomeninges include thickening and opacity of the pia-arachnoid; adhesions make it impossible to strip the meninges without damaging the cortex; in such cases a typical worm-eaten appearance results—the "état vermoulu" of Marie. Section through the cortex in such cases often reveals a peculiar "streaky" appearance, described by Neubürger [72]. This feature usually antedates the "état vermoulu," and is thought to be an earlier stage of the same process.

The weight of the brain is diminished, and in extreme cases it may weigh less than 1,000 grm. Very often there is a convolutional atrophy, which may be universal or localized. In contrast to Pick's disease, however, cortical atrophy never occurs as a solitary pathological manifestation. When the atrophy is more or less localized, the frontal lobe is most often affected, followed next in frequency by the temporal lobe. Some degree of passive ventricular distension always accompanies atrophy of the parenchyma (hydrocephalus *ex vacuo*). Shrinkage of the basal ganglia may be obvious to the naked eye, and may prove histologically to be the result, not of mechanical pressure from the hydrocephalus, but of an actual diminution in the number of cells.

The minute vascular changes consist, firstly, in glial overgrowth, which may be diffuse or patchy. In the latter case the gliosis may be most obvious around the blood-vessels; at other times it appears tangentially in the white matter immediately underlying the cortex (= Binswanger's subcortical encephalitis). Globus [35], who studied the glial changes by the impregnation methods of the Spanish school, found a hyperplasia of the astrocytes. In the areas of softening, however, the astrocytes show every variety of regressive change up to total disintegration. During this process of atrophy their morphological characters may so alter as to resemble the amœboid cells of Alzheimer, or even "gitter" cells. Hortega cells are somewhat increased in number, and appear often in irregular aggregations (germinal centres). Alterations occur in their shape; some constitute the giant microglia cells of Cajal, others develop into true compound granular corpuscles. The oligodendroglia shows a slight generalized hyperplasia, except in the necrotic areas where these cells are few or absent.

Neuronal changes include disappearance of cells. The remaining cells may show shrinkage, nuclear eccentricity and defective absorption of stain. The maximum change is usually found in the third and fifth layers of the cortex. Pigmentary deposits of an argentophil nature are not uncommon. The neurofibrils may be irregularly or uniformly thickened and the individual processes become intermingled (Alzheimer's tangles). Around the blood-vessels there may be an infiltration of small round cells.

Weigert-Pal preparations usually show widespread, though not necessarily intense, alterations in the myelin sheaths. Thus the long fronto-pontine tracts are frequently abnormally pale. The lenticular nucleus is almost always affected, especially the pallidum and its connections, and there is a relative demyelinization in the subthalamic structures.

The changes consequent upon senility comprise some degree of neuronal disappearance, hyperplasia of the connective tissue and increase in the pigmentary elements. The cortical cells tend to disappear early, particularly in the deeper laminæ, and Purkinje cells may be absent from the cerebellar cortex (Bouman [7]). Lastly, the presence of senile plaques in the cortical gray matter is characteristic. Despite the work of Bouman and Bok [8], who found plaques in the basal ganglia in a number of cases (nine out of ten), most writers have stated that the central gray matter is rarely the seat of such change.

There is nothing specific in the character or distribution of the vascular alterations in this particular variety of arteriosclerosis. In most instances the larger arteries of the base show the maximum change, but in a few cases (cf. Claude and Cuel) the capillaries may be affected to a greater degree.

In those cases in which muscle changes, of the type of retractile myosclerosis, are prominent, the pathology is characteristic. Atrophy, pigmentation and plasmodial regression of the muscle fibres are found, and some of the fibres are hypertrophied. The connective tissue lying between the bundles and also between the individual fibres shows an enormous proliferation; fibrous or fatty tissue may replace some of the muscle fibres. Accumulations of small round cells distend the lymphatic spaces.

A number of cases also present evidence of disease in the peripheral nerve-trunks, consisting in parenchymatous degeneration with interstitial overgrowth, due to changes in the small nutritive blood-vessels. The nerve fibres are diminished in number and those that remain show pronounced atrophy. There is an increase in the peri- and endo-neural connective tissue. Changes in the vasa nervorum consist in a thickening of all the coats, especially the intima, and in places the lumen may be entirely blocked.

The distribution of the cerebral lesions in cases of arteriosclerotic Parkinsonism is characterized by an extreme diffuseness. Certain locations, however, are especially liable to be affected. Thus, in every instance the corpus striatum is the seat of widespread morbid change. Each of the constituent nuclei may be diseased, but the frequency with which the globus pallidus and the large striatal cells are affected is striking. The subthalamic centres are rarely specifically mentioned, though they are sometimes stated to be affected to a lesser degree. Certain writers have called attention to the implication of certain parts of the basal ganglia in cases with particular added symptoms; thus, Kleist has drawn attention to lesions in the thalamus in cases in which counterpull was a prominent feature; in Merzbach's cases of arteriosclerotic Parkinsonism, in which various speech iterations were present, there were marked changes in the caudate. Freund and Rotter have emphasized in their cases the presence of lesions in the dentate nuclei.

Where pyramidal and pseudo-bulbar signs were present, additional lesions are demonstrable in the white matter of the hemispheres, the internal capsule and the pons. Lesions in the cerebellum, particularly in the dentate nuclei, have been demonstrated in the cases belonging to the fifth clinical group, and also in some cases (cf. Freund and Rotter) in which no cerebellar signs were demonstrated during life.

The Pathology of Senile "Vorsteifung."

The pathological status of this particular syndrome is not easy to determine. According to Jakob, senile changes are found in the cortex such as plaques and Alzheimer's fibrillary thickenings. There is marked degeneration of the third and fifth layers, especially in the frontal and temporal lobes. In the striatum and pallidum there is a severe diffuse parenchymatous degeneration with glial increase. As in the idiopathic paralysis agitans, the large striatal cells suffer most. Unlike the ordinary case of senile dementia, plaques may occur in the basal ganglia; Alzheimer's tangles are not seen here. The pallidal network is filled with calcareous-like deposits which stain blue-black with hæmatoxylin and do not give a fat reaction. Changes in the locus niger are less severe in degree, but shrinkage of the cells, demyelinization and poverty of melanin are evident. Jakob differentiates this pathological picture from that in Alzheimer's disease by the presence of more severe changes in the striatum and pallidum.

Pathological diagnosis.—From the standpoint of the pathologist, most difficulty lies in distinguishing the arteriosclerotic types of Parkinsonism from idiopathic paralysis agitans and from the syphilitic and post-encephalitic varieties. Although the pathology of the true Parkinson's disease is far from being established, nevertheless there are certain rules which guide in differentiating it from arteriosclerotic Parkinsonism; in general terms, the latter diagnosis is suggested in the presence of any of the following features:—

(1) Naked-eye change in the basal ganglia or midbrain (hæmorrhages, softening, lacunes, "état criblé").

(2) Definite structural change in the walls of the blood-vessels (other than calcification).

(3) A marked degree of glial increase.

(4) Perivascular hæmorrhages.

(5) Lesions of similar type demonstrable elsewhere in the central nervous system (cortex, pons, cerebellum).

Although Löwy, and C. and O. Vogt, were inclined to make the pathological diagnosis of paralysis agitans in the presence of macroscopic foci of disintegration (an "état criblé" of the caudate and lenticular nuclei) this view is not accepted by most other neuropathologists. Changes in the blood-vessels are slight or absent in idiopathic paralysis agitans (Ramsay Hunt, Lhermitte, Foix); and any marked thickening of the vessel wall or proliferation of its cell elements must be regarded with suspicion. An exception must be made in the case of "calcification" in the media and adventitia of the most oral blood-vessels of the globus pallidus—a change which Weston Hurst [39] has shown to occur in 50 per cent. of all brains. Lastly, the presence of a diffuse or scattered pathological process, not confined to the lenticular nucleus or to the subthalamic region, suggests an arteriosclerotic basis.

The pathological differentiation of arteriosclerotic Parkinsonism from syphilitic vascular disease of the striatum hinges on the character of the changes in the vessels and peri-arterial tissue. Thus, the syphilitic cases will be characterized by vascular changes affecting especially the endothelium and by lymphocytic infiltration of the vessel walls with exudation of small round cells into the Virchow-Robin spaces. Moreover, plasma cells are here and there visible, in contrast with the arteriosclerotic cases. In most of the recorded instances other widespread syphilitic lesions have been discovered, particularly in the cortex and spinal cord. It need hardly be pointed out that positive serological evidence of syphilis in no way invalidates the diagnosis of a co-existent arteriosclerotic process, and the cerebro-vascular lesions of a given case may be purely degenerative and not syphilitic, despite a positive Wassermann reaction.

The pathological features of post-encephalitic Parkinsonism are distinct from those of the arteriosclerotic varieties. Absence of high-grade vascular disease (other than "calcification" of the middle coat), absence of naked-eye focal lesions, and the presence of perivascular "cuffing" favour the former diagnosis. Some authorities have stressed the fact that in the post-encephalitic varieties the locus niger tends to be affected to a greater degree and more constantly than the globus pallidus, whereas the converse is sometimes held to be true for the arteriosclerotic types. The point of differentiation is not to be relied upon implicitly, however, as there may be widespread disease of the locus niger in the arteriosclerotic cases.

Pathological discussion.—It becomes obvious when we examine the pathological changes in this syndrome that the subject is bristling with difficulties. Discrepancies become apparent as soon as we cease to focus upon the pallidum and take a comprehensive and commonsense view of the facts.

The first difficulty is the frequent presence of pathological lesions where none were suspected by the clinician; a few examples will suffice. In Urechia and Mihalescu's case, in which a softening was found in the corpus striatum, no striatal symptoms were present during life. Vincent [98] reported foci of softening limited to the lenticular nucleus and to the head of the caudate in a case of an arteriopath who had shown no striatal symptoms. Frets found softening in the oral part of the caudate and putamen, in a patient who had clinically no symptoms referable to the basal ganglia. A case recorded by Freund and Rotter (Group 3, Case 2) was found at autopsy to have, besides the ordinary cortical changes of senile dementia, severe vascular lesions in the pallidum and in the dentate nuclei. Clinically this patient showed only a few symptoms referable to the strio-pallidum, a fact which the authors found difficult to explain. Lastly, one might quote those cases in which severe vascular lesions in the lenticular nuclei have been found after coal-gas poisoning without any corresponding symptoms, and the bilateral pallidal softenings in fatal cases of pneumonia (Hadfield [108]) in which striatal disease was never suspected.

It is arguable, of course, that in some of these instances the examination during life was incomplete and that minor strio-pallidal symptoms might have been overlooked. This is a possibility in some cases, particularly where a state of coma has rendered difficult a neurological examination. But not all the discrepancies can be explained away in this fashion; there still remain cases where full clinical investigations have failed to demonstrate unequivocal basal ganglion symptoms.

Again, in correlating the pathological and clinical data in cases of senility, one is in doubt as to what exactly is understood by the term "normal" old age. Oseki [76], for example, has reported definite pathological lesions (lacunes, gliosis, fatty degeneration of cells) in the corpus striatum of ten senile patients (aged 70-85). All of these were reported as showing no abnormal neurological signs during life, but we do not know whether any distinction was drawn between healthy senescence and pathological senility, and how much rigidity and asthenia, and what degree of akinesis, were regarded as normal.

It may be conceded, therefore, that pathological changes are sometimes present, of which we do not find adequate clinical expression. It is less easy to gauge the frequency of the opposite phenomenon, that is, whether cases occur that clinically suggest striatal disease, which cannot be substantiated pathologically. There are but few cases on record of this anomaly. A similar difficulty is met with where clinical evidences of bilateral disturbances of striatal function have been present although the pathological condition has been that of strictly unilateral disease. Noethe's case is an excellent example; Meissner's case of a right-sided cerebral tumour involving the basal ganglia was associated clinically with a bilateral catatonic-akinetic syndrome.

Of particular interest are those rare instances where a single pathological lesion has given rise to bilateral clinical signs of a different order in the two halves of the body. Thus, a solitary focus in the corpus striatum may be characterized by a contralateral hemiplegia with homolateral catatonic phenomena. In Rieger's case, for instance, a softening in the right corpus striatum was followed by a left hemiplegia and right-sided catatonia, while a patient of Kraepelin's developed, from a single pathological lesion, a contralateral hemiplegia and a homolateral catatonia.

Again, in cases where clinical evidences of bilateral strio-pallidal disease are associated with bilateral striatal lesions, the clinical signs may have been unequal in degree on the two sides without any corresponding anatomical asymmetry. Jakob's first case (No. XI) illustrates this point; in this patient the right side of the body was weaker and more rigid, and the muscles of the right side were harder on palpation, but the intensity of the pathology was approximately equal in the two hemispheres.

It is necessary to recall, moreover, that the presence of anatomical lesions does not necessarily entail abolition of function. Certain pathological changes, such as demyelination, glial increase, or perivascular cell infiltration are not incompatible with physiological activity, and it is not until the process becomes widespread or disseminated, or until there is actual damage to the neuron, that permanent loss of function results. An association with the pathophysiology of disseminated sclerosis is at once suggested. The degree of suddenness with which the pathological changes arise probably influences the resulting clinical picture; thus, abrupt lesions accompanied by œdema and other temporary disturbances in the local vascularity, are probably associated with severe clinical manifestations which are not of permanent character. On the other hand, a gradual and progressive ischæmic process will lead to a permanent and steadily increasing disability. Lastly, in states of partial or relative ischæmia the efficiency of the cerebral circulation will depend on numerous other variants, such as the degree of splanchnic distension, posture, sleep and exercise.

The frequency with which unilateral lesions are seen compared with the rarity of clinical manifestations of arteriosclerotic Parkinsonism confined to one side suggests the question whether bilateral vascular lesions are required before amyostatic symptoms become manifest. It is, of course, well known that a hemiplegic distribution of symptoms is common in paralysis agitans proper, and this probably corresponds to a unilateral pathological change. The nature of the causative lesion, however, is very different in this case; an atrophy of large pallidal cells is essentially a selective or systemic process, and is, unlike the the cruder vascular lesions, superimposed upon a full complement of neurons.

In assessing the probable effect of particular morbid processes it is necessary to recall the patchy nature of certain types of cerebro-vascular disease. As Dunlap [22] has pointed out, in cerebral arteriopathy the striatum may be "peppered" with lesions, each one of which is sufficient to abolish the function of the particular cells affected. The intervening areas are, however, immune and their physiological activities are unimpaired. The "état criblé" and the lacunes of cerebral disintegration are the best illustrations of a dissemination of small lesions with integrity of the intervening structures.

We are dealing, therefore, with a pathological process which is diffuse and which may be present as scattered islets occurring haphazard throughout the nervous system. Each individual focus may or may not be sufficient in itself to cause an alteration in function. There results, therefore, a disability which is probably not equivalent to the algebraic sum of the component lesions. Years ago Hughlings Jackson pointed out that the so-called "double hemiplegia" is not the equal of two hemiplegias, but is that plus something more. The same phenomenon is seen in other types of cerebro-vascular disease. Cerebral arteriopathy may be also compared with disseminated sclerosis, in that both diseases are characterized by a multiplicity of diffuse but discrete lesions with a resulting clinical picture. It is questionable whether one is justified in correlating pathology with clinical findings along purely anatomical avenues; or whether the dissolution of function does not take place along phylogenetic lines, as suggested by Brouwer [11]. If so, one must not expect to correlate a given symptom with a particular lesion; Brouwer has suggested that when the central nervous system is affected by a multiplicity of diffuse lesions the end-result will be in accordance with Jackson's views of evolution and dissolution. Functions which are old in the phylogenetic sense will be spared, whilst the youngest physiological processes will be the first to suffer. A developmental explanation rather than a strictly anatomical one may hold true, therefore, for some of the cases of diffuse cerebro-vascular disease.

An explanation is obviously desirable of those cases in which bilateral clinical signs (either similar or dissimilar) occur as the result of a solitary unilateral lesion. When examined more closely, however, the isolation of the focus is more apparent than real; in other words, there may exist other pathological changes, single or multiple, and probably of a microscopic character, which influence profoundly the effect of subsequent gross lesions. In Rieger's case there was, in addition to a softening in the right corpus striatum, the characteristic pathological evidences of general paralysis; Kraepelin's patient had, besides a single focus of disease, a large internal hydrocephalus affecting the lateral ventricles of both hemispheres. In such cases there are multiple diffuse lesions which, of themselves insufficient to cause physical signs, are immediately made manifest on the addition of a single large focus.

Kleist has put forward an explanation along anatomical lines: the pallidum, (and striatum) send impulses to both sides of the body, but especially to the opposite side, and small unilateral lesions therefore produce no clinical symptoms. On the other hand, larger one-sided lesions produce motor manifestations of contralateral distribution. Bilateral lesions of a gross character produce bilateral signs. Slight lesions in both striata give rise to psychomotor hyperkinetic manifestations in both halves of the body. The combination of a gross lesion in one striatum with a small lesion in the other produces a hemiplegia on the side opposite the larger focus, with psychomotor hyperkinesis of homolateral distribution.

An analogy is found in those rare cases of a contralateral hemiplegia with homolateral grasping and groping, apparently resulting from a single pathological lesion (e.g., Schuster). In such cases there are either multiple minor foci scattered throughout both hemispheres, or (as in the case of tumour) the opposite half of the brain is distorted by hydrocephalus or by direct pressure.

The possibility of correlating with precision the anatomical and clinical data, in view of the many difficulties enumerated, arises at this point. Numerous attempts have been made to deal with the problem, but many of the conclusions are probably too schematic and too plausible. The available facts may be very briefly marshalled.

When senile or arteriosclerotic processes are limited to the cortex we find clinically a state of dementia without physical manifestations of Parkinsonism. Hence it may be argued that the dementia is the expression of cortical change, whether of the nature of senile plaques, cell atrophy or capillary fibrosis. In general terms it may also be stated that the degree of intellectual loss is directly proportional to the severity of the cortical change.

Recently, Rhein, Winkelman and Patten [82] have attempted to correlate the mental conditions in the aged with the anatomical distribution of the changes in the cerebral blood-vessels. Thus they associate disease of the arteries of large calibre with the clinical picture of "arteriosclerotic deterioration." Sclerosis of the small vessels is coupled with a "progressive arteriosclerotic psychosis." Disease of both large and small arteries is associated with "arteriosclerotic dementia." In a fourth group they place those cases in which the arterial changes are fibrotic rather than sclerotic in type; this pathological group comprises individuals whose mental faculties were preserved and the cases fell into the cadre of "senility." Unfortunately, the authors do not deal with the neurological aspect of their subject.

Some of the positive or active manifestations of dementia such as hyperkineses of a complicated or "psychomotor" type; the negativistic manifestations of "counterpull," and diverse movements of clutching, grasping and groping, require explanation. There is but little unanimity here. Earlier workers associated many of these phenomena with disease of the basal ganglia, without specifying any particular localization. Adie and Critchley have, however, referred the grasping movements to disease of the frontal lobe. Schuster, who formerly regarded striatal disorder as their cause, modified his earlier opinion and suggested a combined frontal and striatal dysfunction, the major importance being attached to the frontal lesions. Kleist stated that psychomotor disorders, although frequently associated with changes in the frontal lobes, do not result therefrom, but rather from a disordered balance of function between the individual ganglia of the corpus striatum. Forced grasping and allied phenomena are, in his opinion, part of the wider process of counterpull, which he associates with disease of the thalamus, releasing a lower affective centre in the caudal oblongata.

Further difficulty is encountered in correlating the hypokinetic-hypertonic syndromes with an anatomical basis. Whether it is justifiable to regard akinesis and rigidity as necessarily associated one with the other is doubtful. The whole trend of modern opinion is to the contrary. Foerster says quite definitely: "to identify the hypokinetic (or akinetic) syndrome with rigidity or 'Fixationsspannung' is to ignore the complexity of the problem." It is well known that the two symptoms are not necessarily co-existent, for while akinesis usually accompanies rigidity, it is often demonstrable in cases in which there is no increased tonus, and conversely, a state of pathological restlessness (or akathisia) can accompany a Parkinsonian syndrome. One must, therefore, dissociate these two symptoms for the purpose of discussion. Although it is not correct to associate rigidity entirely with poverty of movement, one is probably justified in regarding hypokinesis as part of the bradykinetic syndrome of Cruchet.

Most continental writers (Lotmar [63], C. and O. Vogt [99], Kleist), have tended to associate the Parkinsonian akinesis with a disappearance of the large cells of the striatum, or of the locus niger, or both. Thus, Kleist correlates poverty of associated and single movements, particularly those occurring in the periphery of the limbs and in the face, with disease of the locus niger, and especially the zona reticularis. On the other hand, disease of the caudate and external pallidum produces a diminution or absence of the higher expressive and symbolic automatisms. Jakob associates akinesis with disease of the small ganglion cells of the striatum. Lewy has departed somewhat from the traditional views in suggesting that part at least of the hypokinesia in Parkinsonism results from disease of the frontal lobes.

It is obvious, moreover, that akinesis is a manifestation of many types of nervous and even extraneural disease. A striking paucity of movement (thought not paralysis) can occur in cerebellar disease, in lesions of the sensory cortex, in stuporose states, as well as in painful and other affections of the peripheral nerves, muscles and joints. Kinnier Wilson is emphatic on this point: . . . . "akinesis, or poverty of movement," he states, "obviously may arise at one or more of the lower, middle or highest physiological neural levels (in Hughlings Jackson's sense), a possibility which renders invalid its ascription to the corpus striatum alone."

The question of rigidity in arteriosclerotic Parkinsonism has already been discussed, and it has been emphasized that besides the pallidal component (resulting from the loss of the large striatal cells) other important factors contribute to the increased tonus. One recalls, too, that Stief quotes Jakob and the Vogts in suspecting cortical changes of contributing to the rigidity in cases of Parkinsonism. There is abundant pathological evidence linking disease of the palæostriatum with the appearance of a distinctive type of rigidity. One interesting point for discussion hinges, however, on the relative importance of pallidal as opposed to nigral changes. Whereas the former are the more obvious in idiopathic Parkinsonism, the latter are all-important in the post-encephalitic varieties.

In the arteriosclerotic types co-existent changes in both pallidum and locus niger are often described. But in certain instances it is clear that pallidal lesions may exist without any corresponding disease of the locus niger. There is only one record of the opposite condition, namely, morbid processes in the locus niger with a healthy pallidum, in a case of arteriosclerotic Parkinsonism (cf. Case 5, Freund and Rotter). The close anatomo-physiological and developmental association between these two structures renders controversy as to their relative importance of theoretical rather than of practical value.

Some authorities have considered the hypertonic-akinetic syndrome as a whole and have carried the process of correlation still further. Kleist, for example, considers striatal function as follows: (1) gross automatisms (i.e. mass movements of the whole body) are regulated by the subthalamic structures and the internal pallidum; (2) finer automatisms belong to the putamen and locus niger; and (3) finest automatisms (expressive and symbolic movements) are subserved by the caudate and external pallidum. Symptoms due to lesions of groups (1) and (2) cause "myostatic disorders," whereas affections of (3) produce "psychomotor" disturbances.

Kleist goes further, and supports Jakob and C. & O. Vogt in ascribing to the basal ganglia a somatotopy, or anatomical representation of body segments. Thus the head, face and the organs of speech are said to lie farthest forward in the most cephalad segments of the pallidum, putamen and caudate, followed next by arm and trunk, the leg centres being the most caudal.

Other views have been held with regard to the pathogenesis of the arteriosclerotic rigidity-syndrome, besides involvement of the striatum. It will be recalled that Foerster originally suggested disease of the cerebellum and its connections. In his later communications Foerster refers to his earlier belief and points out the many clinical resemblances between the arteriosclerotic rigidity and syndromes of fronto-ponto-cerebellar origin (hypokinesis, rigidity, flexor attitudes, bradykinesis, catatonia).

An interesting point has been raised by Freund and Rotter. They believe the pathological process in some of their cases to represent a hitherto undescribed combined system-disease of the strio-pallidal-dentate-rubral-peduncular pathways. In this way the red nucleus is cut off from strio-pallidal as well as from cerebellar influences. The authors speculate as to the possible clinical significance of a physiological isolation of the red nucleus (cf. Munk's "Isolierungsprinzeps.")

Certain interesting problems arise regarding the origin of the early and severe joint and periarticular changes in cerebral arteriosclerosis. We have already hinted at an association between chronic arthritis deformans and a state of pseudo-Parkinsonism, a connection which, since the writings of Charcot, has received no little attention in France. A detailed study of "le syndrome pallidal du rheumatisme chronique déformant," as it is called, would be beyond the scope of this paper, except in its relationship with the arteriopathic types. Contractures and joint changes appear early and may become severe in cases of arteriosclerotic Parkinsonism, and the possibility arises as to whether these complicating features are determined solely by decubitus, faulty nursing and other similar factors. It is conceivable that the presence of cerebral disease has a more direct and causal relationship. Foerster, in describing the anomalies of attitude and the deformities of the hands and extremities in this syndrome, believes they exist independently of contractures, and are due to an independent, specific, flexing factor. Freund and Rotter [30] affirm quite definitely that in extrapyramidal manifestations of advanced age joint deformities of cerebral origin occur, which in outward form simulate those of chronic progressive polyarthritis.

It is obvious from a consideration of the foregoing attempts at associating anatomical and clinical data that no satisfactory conclusion is possible. Indeed it is fair to say that the study of arteriosclerotic Parkinsonism has so far thrown little light upon the problem of striatal physiology, and in view of the difficulties peculiar to cerebral arteriosclerosis in correlating structural with functional change, it is doubtful whether any great help is to be expected in this direction.

Such information as has been available tends to argue against a conception of the corpus striatum as the sole, or even the most important, site of disease in arteriosclerotic rigidity-syndromes. This view confirms Kinnier Wilson's views expressed as follows: . . . "my clinical studies have impressed me with the belief . . . that striatal symptomatology and function must be comparatively simple; and they have forced me to the conclusion that the unwieldy and top-heavy symptom-complex which has gradually come to be erected on the ganglia must be vigorously stripped of non-essentials."

Senile Rigidity; Inter-relationship with Senility, Dementia, Arteriosclerotic Rigidity and Parkinson's Disease.

Other problems present themselves for discussion at this stage, and the claims of Jakob's senile rigidity as a clinical entity will require consideration. Secondly, the relationship of this syndrome to other varieties of Parkinsonism (both idiopathic and arteriosclerotic) and the association of these diseases with senility and senile dementia afford interesting speculation. Some have actually assumed a unitary conception for these morbid states, associating them with an identical pathogenic basis, namely, an involutional process differing only in its anatomical location.

The question of the status of Jakob's disease may be considered first. Jakob isolated certain types of senile dementia, closely allied to Alzheimer's disease, in which rigidity is a prominent manifestation. In such cases the pathological changes are dominant in the striatal parenchyma; cortical processes of simple senile dementia are also demonstrable but in lesser degree. Lhermitte, however, is opposed to the isolation of a senile variety of rigidity from the arteriosclerotic types; mental enfeeblement, he points out, may be equally conspicuous in the arteriopathic type of pallidal rigidity. But Lhermitte does not discuss the propriety of considering under the title of senile muscular rigidity those cases in which no clinical or pathological evidence of arteriosclerosis is forthcoming. Such cases cannot be classed as arteriosclerotic Parkinsonism. They differ too from idiopathic paralysis agitans in their later onset, the absence of tremor, and the outstanding dementia which often antedates the pallidal signs. The pathological differences centre in the relative severity of cortical changes.

The akinetic-hypertonic senility-syndromes may be regarded as exaggerations of the physiological movement disorders of old age. As Stief points out, the frontiers between physiological and pathological activities (the "physioklise" and "pathoklise" of the Vogts) are here particularly intangible.

We may now pass to the relationship between senile processes and the occurrence of dementia, arteriosclerotic Parkinsonism and paralysis agitans. An all-important problem naturally arises as to the relationship between senile and arteriosclerotic processes in general; whether the cerebrum is actually as old as its blood-vessels; or whether the pathological changes of the senium are distinct from those of the cerebrovascular system. All the evidence goes to suggest that the structural changes of old age are independent of arterial degeneration. Although frequently associated, the senile brain and the arteriopathic brain are independent entities. As Stief remarks, the ageing of the central nervous system is a process *sui generis* associated with, but not dependent upon, the old age changes in the vascular system.

It is clear, therefore, that there must be distinctions between senile and arteriosclerotic dementia, and between senile and arteriosclerotic Parkinsonism. The frontiers are ill-defined, however, and the two processes are so often combined that it obviously becomes difficult at times to relegate a particular case to its proper category. All who have studied the subject, whether along clinical or pathological lines, insist that there are transition forms between the various involutional disorders of the strio-pallidum and cortex. Jakob speaks of intermediate clinical and histological types which link up paralysis agitans, via Alzheimer's disease, with senile rigidity plus dementia on the one hand, and on the other with arteriosclerotic rigidity. Stief is inclined to place paralysis agitans among the neurological manifestations of senility. In this way he associates himself with the conception of Jelgersma and Lewy in regarding Parkinson's disease as the result of senile disintegration with fortuitous incidence upon the basal ganglia. The involutional disorders of the cerebrum may, therefore, be grouped according to their location into the following schema of Stief's:—

(*a*) Predominating in cortex .. = *Senile dementia*
(*b*) Predominating in basal ganglia = *Paralysis agitans* (*without psychosis*).
(*c*) Affecting cortex and basal ganglia = *Senile chorea. Paralysis agitans with mental change. Senile rigidity. Alzheimer's disease.*

In the latest exposition of the pathology and genesis of Parkinson's disease, Foix and Nicolesco [27] take up an open attitude with regard to the association with old age. They make the statement, however, that paralysis agitans appears at times as the result of an abnormal localization of the processes of senility.

CONCLUSIONS.

The object of this communication is to draw attention to a variety of Parkinsonism due to cerebral arteriosclerosis.

Although cerebro-vascular disease may give rise to the complete picture of Parkinson's disease, incomplete forms are commoner. All gradations occur, from the mildest degree of hypokinesis and hypertonus (= arteriosclerotic rigidity) up to forms which are barely distinguishable from classical paralysis agitans.

For convenience of description one may subdivide the cases of arteriosclerotic Parkinsonism into five clinical types; (1) early cases characterized by some immobility of expression and short-stepping gait; (2) cases forming part of the pseudo-bulbar syndrome; (3) cases associated with marked intellectual defect; (4) pyramido-pallidal syndromes; and (5) cerebello-pallidal syndromes.

There are several clinical points of distinction between the arteriosclerotic varieties of Parkinsonism and cases of idiopathic paralysis agitans:—

Symptoms may commence suddenly in the arteriosclerotic cases, although an insidious onset is more usual. The progression is more rapid and may proceed by a series of abrupt exacerbations.

The age of onset is approximately the same in the two conditions, but an unusually early or a very late age for commencement of symptoms suggests a vascular basis.

In the arteriopathic cases tremor is usually absent; the muscles feel firmer to the touch; and the rigidity is often characterized by a superadded tendency towards catatonia.

Many of the arteriosclerotic cases (e.g., those in Group 2) have "bulbar" signs and emotional incontinence. A large number, too, show a more or less profound dementia.

The presence of other focal cerebral symptoms (of aphasic, apraxic, cerebellar or pyramidal nature) argues in favour of an arteriosclerotic basis.

Evidence of disease in the cerebral or peripheral blood-vessels is present in the arteriosclerotic varieties; the blood-pressure is often high, but in the senile or decrescent types of arterial degeneration the tension may be low.

The pathological appearances vary greatly in character and diffuseness; the essential features comprise lesions in the globus pallidus, and, to a lesser extent, in the substantia nigra, directly consequent upon vascular disease.

Pallidal lesions must not be regarded as the sole responsible agents in the clinical appearances, for changes at other levels can be demonstrated as contributing towards the rigidity. Thus, mental impairment, pyramidal disease, changes in the peripheral nerves, and in the muscles, tendons, joints, and blood-vessels of the extremities, all play a part in producing a hypertonic-hypokinetic syndrome.

By isolating an arteriosclerotic variety, support is given to the conception of Parkinsonism as a syndrome which may occur under numerous pathological circumstances. It is the site, rather than the nature of the disease, which produces the characteristic clinical picture.

In conclusion, it is a pleasure to express my indebtedness to Dr. S. A. Kinnier Wilson for his kind and valuable criticisms. My thanks are also due to Drs. Collier, Holmes, Walshe and Feldman for permitting me to quote cases under their care.

REFERENCES.

[1] Adie, W. J., and Critchley, M. "Forced Grasping and Groping," *Brain*, 1927, **50**, 142.

[2] Alzheimer. "Die Seelenstörungen auf arteriosklerotischen Grundlage," *Allg. Zeitschr. f. Psychiatr.*, 1902, **59**, 695.

[3] Babinski, J. "Quelques documents relatifs à l'histoire des fonctions de l'appareil cérébelleux et de leurs perturbations," *Rev. Mens. de Méd. Int. et de Thérap.*, 1909 (May), p. 6.

[4] Bard, L. "Des contractures post-hémiplégiques pseudoprécoces," *Sem. Méd.*, 1907, **27**, 61.

[5] v. Bechterew. "Hemitonia post-apoplectica," *Deutsch. Zeitschr. f. Nervenheilk.*, 1899, **15**, 437.

[6] Boettiger. "Ueber extracapsuläre Hemiplegien inbesondere über 'Hemihypertonia apoplectica,'" *ibid.*, 1921, **68-69**, 165.

[7] Bouman, L. "Die Axonschwellungen der Purkinjeschen Zellen, inbesondere bei Dementia Senilis," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1928, **113**, 379.

[8] Bouman, L., and Bok, S. T. "Senile Plaques im Corpus Striatum," *ibid.*, 1923, **85**, 164.

[9] Brissaud, E. "Leçons sur les maladies nerveuses," Paris: Masson, 1895, p. 486.

[10] *Idem.* "Leçons," 2me série, Paris: Masson, 1899, p. 305.

[11] Brouwer, B. "Anatomical, Phylogenetical and Clinical Studies on the Central Nervous System," Baltimore, 1927.

[12] Buzzard, E. F., and Barnes, S. "A Case of Chronic Progressive Double Hemiplegia," *Rev. Neurol. and Psychiatr.*, 1906, **4**, 182.

[13] Catola. "Étude clinique et anatomo-pathologique sur les lacunes de désintégration cérébrale," *Rev. de Méd.*, 1904, **24**, 778.

[14] Claude, H., and Alajouanine, Th. "Hypertonie généralisée avec troubles d'aspect pseudobulbaire, rire et pleurer spasmodique chez un adulte: Localisation pallidale probable," *Rev. Neur.*, 1922, **29**, 567.

[15] Claude, H., and Cuel, J. "La meiopragie cérébrale par angiosclérose précoce sans ischæmie en foyer (forme de démence présenile artério-scléreuse), *L'Encéphale*, 1927, **22**, 161.

[16] Collins, J. "A Case of Cortical Cerebral Arterio-sclerosis with Distinct Focal Symptoms," *The Post-Graduate*, 1905, **20**, 465.

[17] *Idem.* "A Definite Clinical Variety of Cerebral Arteriosclerosis," *Journ. Nerv. and Ment. Dis.*, 1906, **33**, 750.

[18] Cones, W. Pearce. "Note on a Case of Paralysis Agitans and Cerebral Arteriosclerosis," *Bost. Med. and Surg. Journ.*, 1911, **164**, 755.

[19] Critchley, M. "On Palilalia," *Journ. Nerv. and Psychopath.*, 1927, **8**, 23.

[20] Crouzon, Dereux and Kenziger. "Paralysie pseudobulbaire d'origine protuberantielle (association d'un syndrome pseudobulbaire et d'un syndrome cérébelleux)," *Rev. Neur.*, 1925, **32**(**2**), 747.

[21] Demole, V. "Catatonie expérimentale," *ibid.*, 1927, **34**(1), 861.

[22] Dunlap, C. B. "Structural Changes in Huntington's Chorea," *Brain*, 1927, **50**, 631.

[23] Farran-Ridge, C. "Some Symptoms referable to the Basal Ganglia occurring in Dementia Præcox and Epidemic Encephalitis," *Journ. Ment. Sci.*, 1926, **72**, 513.

[24] Ferrand, J. "Essai sur l'hémiplégie des vieillards," *Thèse de Paris*, 1902.

[25] Foerster, O. "Die arteriosklerotische Muskelstarre," *Allg. Zeitschr. f. Psychiatr.*, 1909, **66**, 902.

[26] *Idem.* "Zur Analyse u. Pathophysiologie der striaren Bewegungsstörungen," *Zeitschr. f. d. ges. Neur. u. Psychiatr.*, 1921, **73**, i.

[27] Foix, Ch., and Nicolesco, J. "Les noyaux gris centraux et la région mésencéphalo-sous optique," Paris: Masson, 1925.

[28] Franceschi, F. "Polineurite et arterio-sclerosi del sistema nervoso centrale e periferico," *Riv. di Pat. nerv. e ment.*, 1903, **8**, 193.

[29] Freund, C. S., and Rotter, R. "Extrapyramidale Bewegungsstörungen im hoheren Alter," *Arch. f. Psych.*, 1927, **81**, 5.

[30] *Idem.* "Ueber extrapyramidale Erkrankungen des höheren Alters mit einem Beitrag zur Pathogenese seniler Parenchymveranderungen," *Zeitschr. f. d. ges. Neur. u. Psychiatr.*, 1928, **115**, 198.

[31] Fumet, P. "Contribution à l'étude des myopathies séniles primitives," *Thèse de Paris*, 1922.

[32] Garbini, G., and Rossi. U. *Annali di Manicomio provinciale di Perugia*, 1909, **3**, 140.

[33] Gaussel, A. "Contractures précoces et permanentes dans un cas d'hémiplégie de l'adulte," *Nouv. Icon. de la Salpêtr.*, 1905, **18**, 241.

[34] van Gehuchten, P. "Hémiplégie avec aspect figé de la face," *Rev. Neur.*, 1925, **32**(**2**), 794.

[35] Globus, J. H. "Glia Response in Chronic Vascular Disease of the Brain," *Arch. Neur. and Psych.*, 1928, **20**, 14.

[36] Golla, L. "The Objective Study of Neurosis" (Croonian Lecture), *Lancet*, 1921, **2**, 115, 215, 265, 373.

[37] Hall, A. J. "Rate of Movement in Post-encephalitic Parkinsonism," *ibid.*, 1927, **2**, 1009.

[38] Holmes, G. "On Certain Tremors in Organic Cerebral Lesions," *Brain*, 1904, **27**, 327.

[39] Hurst, E. Weston. "On the So-called Calcification in the Basal Ganglia of the Brain," *Journ. Path. and Bact.*, 1926, **29**, 65.

[40] Jackson, J. Hughlings. "Softening of the Brain," *Lancet*, 1875, **2**, 335.

[41] *Idem.* "On Cerebral Paresis or Paralysis with Cerebellar Tremor or Rigidity." *Med. Examiner*, 1878, **3**, 266.

[42] Jakob, A. "Die extrapyramidale Erkrankungen," Berlin: Julius Springer, 1923, p. 126.

[43] James, G. W. B. "Cerebral Arteriosclerosis," *Proc. Roy. Soc. Med.* (Sect. Psych.), 1926, **19**, 30.

[44] Janischewsky, A. "Un cas de maladie de Parkinson avec syndrome pseudo-bulbaire et pseudo-ophthalmoplégique. Quelques considérations sur la pathogène de cette maladie," *Rev. Neur.*, 1909, **17**, 823.

[45] Jarkowski, J. "Kinésie paradoxicale des Parkinsoniens," Paris: Masson, 1925.

[46] Kashida. "Ueber Gehirnarteriosklerose des fruher Alters, und ueber die Kombination von corticalen, pyramidalen u. extrapyramidalen Symptomen bei der Gehirnarteriosklerose," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1924, **94**, 659.

[47] Kleist, K. "Die psychomotorischen Storungen u. ihr Verhältniss zu den Motiliäts-storungen bei Erkrankungen der Stammganglien," *Monatsschr. f. Psychiatr. u. Neurol.*, 1922, **52**, 253.

[48] *Idem.* "Bewegungsstörungen u. Bewegungsleistungen der Stammganglien des Gehirns," *Die Naturwissenschaften*, 1927, **15**, 973.

[49] *Idem.* "Gegenhalten (motorischen Negativismus) Zwangsgreifen u. Thalamus Opticus," *Monatsschr. f. Psychiatr. u. Neurol.*, 1927, **65**, 317.

[50] Lejonne, P., and Lhermitte, J. "Étude sur les paraplégies par rétraction chez les vieillards," *Nouv. Icon. de la Salpêt.*, 1906, **19**, 255.

[51] Ley, R. A. "Forme atypique d'atrophie cérébelleuse ayant évolué en syndrome rigide," *Journ. de Neur. et de Psych*, 1925, **25**, 92.

[52] Lhermitte, J. "Sur une forme spéciale de myopathie sénile," *Trib. méd.*, 1906.

[53] *Idem.* "Etude sur les paraplégies des vieillards," *Thèse de Paris*, 1907.

[54] *Idem.* "Les syndromes striées du vieillard," *Rev. Neur.*, 1922, **29**, 406.

[55] *Idem.* "La myosclérose retractile des vieillards et ses rapports avec le syndrome acinéto-hypertonique," *L'Encéphale*, 1928, **23**, 89.

[56] *Idem.* "La striatite syphilitique primitive," *La Médecine*, 1928, **9**, 349.

[57] Lhermitte, J., and Cornil, L. "Syndrome strié à double expression symptomatique; pseudobulbaire et parkinsonienne," *Rev. Neur.*, 1921, **28**, 299.

[58] *Idem.* "Recherches anatomiques sur la maladie de Parkinson," *ibid.*, 1921, **28**, 587.

[59] Lhermitte, J., and Cuel, L. "Forme ponto-cérébelleuse de la paralysie pseudobulbaire," *ibid.*, 1921, **28**, 364.

[60] Lhermitte, J., and Kyriaco, N. "La forme ponto-cérébelleuse de la paralysie pseudobulbaire," *Gaz. des Hôp.*, 1927 (vol. centennaire), 69.

[61] Lhermitte, J., and McAlpine, D. "A Clinical and Pathological Résumé of Combined Disease of the Pyramidal and Extra-pyramidal Systems, with Special Reference to a New Syndrome," *Brain*, 1926, **49**, 157.

[62] Liljestrand, G., and Magnus, R. "Ueber die Wirkung des Novokains auf den normalen u. den tetanusstarren Skelettmuskel u. über die Entstehung der lokalen Muskelstarre beim Wundstarrkrampf," *Arch. f. d. ges. Physiol.*, 1919, **176**, 168.

[63] Lotmar, F. "Die Stammganglien u. die extrapyramidalemotorischen Syndrome," Berlin : Springer, 1926.

[64] Mackintosh, Ashley. "Bulbar Symptoms in Paralysis Agitans," *Scott. Med. and Surg. Journ.*, 1903, **13**, 325,

[65] Marie, P., and Foix, Ch. "Les syncinésies des hémiplégiques," *Rev. Neur.*, 1916, **23**(**1**), 3, and **23**(**2**), 145.

[66] Marinesco, G. "Contributions à l'étude de l'encéphalite épidémique," *ibid.*, 1921, **28**, 11.

[67] Marinesco, G., and Nicolesco, M. "À propos des modifications du tonus postural et de l'apparition du signe de Babinski consécutive aux injections de scopolamine dans les hypertonies extrapyramidales," *ibid.*, 1927, **34**(**1**), 246.

[68] Martini, P., and Isserlin, A. "Paralysis Agitans, Tetanie und Arteriosklerose," *Klin. Wochenschr.*, 1922, **1**, 510.

[69] Mella, H., and Katz, S. E. "Neurosyphilis as an Etiological Factor in the Parkinsonian Syndrome," *Journ. Nerv. and Ment. Dis.*, 1924, **59**, 225.

[70] Merzbach, A. "Die Sprachiteration u. ihre Lokalisation bei Herderkrankungen des Gehirns," *Journ. f. Psychiatr. u. Neurol.*, 1928, **36**, 210.

[71] Monier-Vinard and Dalsace. "Syndrome pallidal," *Rev. Neur.*, 1921, **28**, 371.

[72] Neubürger, K. "Ueber streifenformige Erkrankungen der Grosshirnrinde bei Arteriosklerose," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1926, **101**, 452.

[73] Newmark, L. "A Lesion in the Putamen," *Journ. Nerv. and Ment. Dis.*, 1919, **49**, 97.

[74] Noethe. "Ueber einen Fall von motorischen Apraxie," *Arch. f. Psychiatr.*, 1913, **52**, 1043.

[75] Orzechowski. "De l'ataxie dysmétrique des yeux," *Journ. f. Psychiatr. u. Neurol.*, 1927, **35**, 1.

[76] Oseki. "Ueber die Veranderungen des Striatums in normalen Senium," *Arbeit. neurol Instit. Wiener Univ.*, 1924, **26**, 339.

[77] Pfeiffer, R. "Ein klinischer Beitrag zur Lehre von der Hemitonia Apoplectica (Bechterew)," *Neurol. Centralbl.*, 1901, **30**, 386.

[78] Pickett, W. C. "A Case of Arteriosclerosis of the Nervous System," *Journ. Nerv. and Ment. Dis.*, 1905, **32**, 182.

[79] Pineas, H. "Klinischer u. anatomischer Befund eines Falles von Kohlenoxydvergiftung," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1924, **93**, 47.

[80] Raymond, F., and Alquier, L. "Sur un cas de paralysie pseudobulbaire," *Nouv. Icon. de la Salpêt.*, 1907, **20**, 371.

[81] Reiter, P. J. "Extrapyramidal Motor Disturbance in Dementia Præcox." *Acta Neuro-Psych.*, 1926, **1**, 287.

[82] Rhein, J. H. W., Winkelman, W., and Patten, C. A. "Mental Conditions in the Aged," *Arch. Neurol. and Psychiat.*, 1928, **20**, 329.

[83] Rosenfeld. "Ueber Skopolaminwirkungen am Nervensystem," *Munch. med. Wochenschr.*, 1921, **31**, 971.

[84] Rowland, R. "On the Nature and Treatment of Softening of the Brain," London, 1851.

[85] Schlesinger, H. "Ueber eine durch Gefässerkrankungen bedingte Form der Neuritis," *Neurol. Centralbl.*, 1895, **14**, 578 and 634.

[86] Schuster, P., and Pinéas, H. "Weitere Beobachtungen uber Zwangsgreifen u. Nachgreifen und deren Beziehungen zu ähnlichen Bewegungsstorungen," *Deutsch. Zeitschr. f. Nervenheilk.*, 1926, **91**, 16.

[87] Sicard, J. A. "Parkinsonisme et rheumatisme chronique," *Rev. Neur.*, 1921, **28**, 682.

[88] Sicard, J. A., and Paraf. "Syndrome strio-pyramidal," *ibid.*, 1921, **28**, 295.

[89] Signorelli, E. "Patogenesi del nistagmo palato-faringo-laringeo. Contributo anatomo-clinico," *Riv. di Patol. nerv. e ment.*, 1927, **32**, 441.

[90] Souques, M. A. "Formes cliniques des syndromes parkinsoniens," *Rev. Neur.*, 1921, **28**, 562.

[91] Steck, H. "Les syndromes extrapyramidaux dans les maladies mentales," *Arch. suisses de Neur. et de Psych.*, 1926, **19**, 195; *ibid.*, 1927, **20**, 92.

[92] Stief, A. "Beiträge zur Histopathologie der senilen Demenz, mit besonderer Berucksichtigung der extrapyramidalen Bewegungstorungen," *Zeitschr. f. d. ges. Neur. u. Psychiatr.*, 1924, **91**, 879.

[93] Stoddart, W. H. B. "Motor Symptoms of Mania and Melancholia," *Lancet*, 1904, **1**, 639.

[94] Urechia, C. I. "La Syphilis peut-elle reproduire le Syndrome de Parkinson?" *Rev. Neur.* 1921, **28**, 584.

[95] Urechia, C. I., Mihalescu, S., and Elekes, N. "La rigidité artério-scléreuse et le syndrome pyramido-pallidal," *Arch. Internat. de Neurol.*, **42**, 161,

[96] Urstein. [Quoted by P. J. Reiter. "Nogle Undersøgelser over Sukkerstofskiftet ved Psychoser," København: Levin and Munksgaard, 1925.]

[97] Verger, H., and Cruchet, R. "Les états parkinsoniens et le syndrome bradykinétique," Paris: Baillière et Fils, 1925.

[98] Vincent, Cl. "Foyers de ramollissement limités au noyau lenticulaire et à la tête du noyau caudé—Aucun symptôme strié," *Rev. Neur.*, 1925, **32**, 194.

[99] Vogt, C. and O. "Zur Lehre der Erkrankungen des striären Systems," *Journ. f. Psychiatr. u. Neur.*, 1920, **25**, 631.

[100] Walshe, F. M. R. "Observations on the Nature of the Muscular Rigidity of Paralysis Agitans and on its Relationship to Tremor," *Brain*, 1924, **47**, 159.

[101] *Idem.* "On Variation in the Form of Reflex Movements, notably the Babinski Plantar Response, under Different Degrees of Spasticity and under the Influence of Magnus and de Kleijn's Tonic Neck Reflex," *Brain*, 1923, **46**, 281,

[102] Wilson, S. A. Kinnier. "Disorders of Motility and Muscle Tone" (Croonian Lectures), *Lancet*, 1925, **2**, 1, 53, 169, 215, 268.

[103] *Idem.* "Modern Problems in Neurology." London: Arnold, 1928, p. 200.

[104] Wilson, S. A. Kinnier, and Cobb, S. "Mesencephalitis syphilitica," *Journ. Neur. and Psychopath.*, 1924, **5**, 44.

[105] Wladyczko, S. "Catatonie comme conséquence des troubles organiques des noyaux gris centraux," *Folia Neuropath.*, Estonia, 1925, **3**, 1;

[106] Wohlfahrt, S. S. "Pallido-striäre Symptome bei Lues in den basalen Ganglien des Gehirns," *Zeitschr. f. d. ges. Neur. u. Psychiatr.*, 1927, **108**, 115

[107] Young, A. W. "A Clinical Analysis of an Extra-pyramidal Syndrome: Paralysis Agitans plus Post-encephalitic Parkinsonism," *Journ. Neur. and Psychopath.*, 1927, **8**, 9.

[108] Hadfield. "Siderosis of the Globus Pallidus; its Relation to Bilateral Necrosis," *Journ. Pathol. and Bacteriol.*, 1929, **32**, 135.

A CASE OF THE PROGRESSIVE HYPERTROPHIC POLYNEURITIS OF DEJERINE AND SOTTAS, WITH PATHOLOGICAL EXAMINATION.

BY R. S. DE BRUYN
AND
RUBY O. STERN.

(From the Wards of Guy's Hospital and the Pathological Laboratory of the National Hospital, Queen Square.)

INTRODUCTION.

THIS disease, of which we have a new example to describe, is undoubtedly a rare one. We have been able to find in the literature only twelve cases with histological verification, and besides these fourteen clinical records. Of these latter, six, as we shall point out later, are of doubtful value.

The history of the disease begins with a paper by Dejerine and Sottas [3] in 1893, whose heading we quote in full so that we may explain our own choice of title. Their title reads "Sur la névrite interstitielle, hypertrophique et progressive de l'enfance, affection souvent familiale et à début infantile, caractérisée par une atrophie musculaire des extrémités, avec troubles marqués de la sensibilité et ataxie des mouvements, et relevant d'une névrite interstitielle hypertrophique à marche ascendante, avec lésions medullaires consécutives." Many of the cases since recorded depart in various particulars from this description. On the pathological side the term interstitial would seem to be misleading, for the characteristic lesion is not so much the increase of interstitial tissue as the hypertrophy of the sheath of Schwann. On the clinical side some writers (e.g., Boveri [1]) have laid particular stress upon the familial incidence and have called the disease "familial hypertrophic neuritis." This departure from the views of Dejerine and Sottas, who did not regard the disease as *essentially* familial, has not been justified by later reports. Cases have been recorded which like our own have begun in adult life, so that if the title is to be inclusive the qualification "de l'enfance" must be abandoned.

In all the cases which we shall review the clinical picture has been that of a progressive polyneuritis, and hypertrophy of the peripheral nerves, if not definitely recorded during life, has been present post mortem. The title "Progressive Hypertrophic Polyneuritis" appears to us therefore the most suitable.

CLINICAL LITERATURE.

At the time when Dejerine and Sottas wrote their paper, Charcot and Marie and Tooth had recently described that form of progressive muscular atrophy which bears their joint names. Dejerine and Sottas, in a review of the literature of this disease, emphasized the points of similarity with and difference from that which they were about to describe. Their two patients were a woman of 45 (with post-mortem examination) and a man of 33—brother and sister. The two remaining brothers in the family were unaffected.

Case 1.—In the first case, that of the woman, some difficulty in walking had been observed from childhood, and at the age of 12 she had orthopædic treatment for her deformed feet. Wasting and weakness of the lower limbs were slowly progressive. The upper limbs were involved some years later. She had occasional pains of lightning character in the left thigh. She married at 32 and had one healthy child. On examination, within three years of her death, the following were the outstanding clinical features:—

Muscular atrophy of a peripheral type: both lower limbs below the knees were almost completely paralysed; the thighs were less severely affected; the hands had atrophied but were not completely paralysed; the fore-arms were slightly affected, but the remaining musculature was normal.

Sensory disturbance of a glove and stocking distribution, with loss to light touch up to the level of the upper third of both lower limbs and on both hands; reduction up to groins and axillæ, and blunting of sensibility to pain and temperature, with retarded transmission of sensation, gradually diminishing from the periphery to the root of each limb. The sense of position was impaired in the upper and lower limbs.

The tendon-jerks were all abolished and the plantar responses were absent.

The electrical reactions showed no response to faradism in the legs, thighs and hands, and a sluggish response in the fore-arms. To galvanism a sluggish response was obtained without inversion of formula.

Pupils.—The left eye had been operated upon for cataract. The right pupil was small. The reaction to light was preserved, but extremely slow and often difficult to observe.

Fibrillation was observed at times in the muscles of the limbs and also in the lower part of the face.

The other features recorded were: slight nystagmus on lateral fixation, inco-ordination in voluntary movements of the upper limbs and a marked kypho-scoliosis. The patient's mentality was somewhat childish. The genito-urinary functions were normal.

No hypertrophy of the peripheral nerves was noted during life.

Case 2.—In their second case kypho-scoliosis was known to have been present since the age of 5. Difficulty in walking was first noticed at 15 and was progressive. About the same time the patient began to suffer with lightning pains, chiefly in the lower limbs but also in the upper limbs. Wasting and weakness of the hands compelled him to give up his work as a printer. His speech became scanning. At the age of 24 he acquired syphilis.

Clinical examination at the age of 30 showed muscular atrophy and sensory disturbance of a type and distribution similar to that already observed in his sister. As in her case, the tendon-jerks were abolished and the plantar responses were absent.

The muscles of the thighs, legs and fore-arms gave no response to faradism. The pupils were small, unequal, irregular in outline and their reactions were of the Argyll-Robertson type. Fibrillation was observed in the muscles of the limbs and of the face. As in the other case, slight nystagmus was present, but was associated in this instance with scanning speech, and with more evident inco-ordination of voluntary movements in the upper limbs. A considerable degree of deafness was present, which had been progressive for some years. Kypho-scoliosis was a marked clinical feature. Mentality was subnormal. The genito-urinary functions were normal.

No hypertrophy of the peripheral nerves was noted until after the discovery of this feature at the autopsy on his sister; the patient was then re-examined, with especial attention to this point, and it was observed that all the accessible nerve trunks were increased in volume, of a diameter twice the ordinary, and very hard to palpation.

The résumé of these cases has been made in some detail in order that certain points may be stressed in the conception held by Dejerine and Sottas of the disease which they were the first to describe. The clinical picture is essentially that of a severe progressive polyneuritis with the disturbance of motor, sensory and reflex function which one would expect in such a condition. The hypertrophy of the nerves was by no means a striking feature of either case. In the first it was discovered only post mortem, and in the second only after this post-mortem discovery had led to a particular search for hypertrophy in the nerve-trunks of the survivor. The Argyll-Robertson pupils observed in the second case may reasonably be attributed to the syphilitic infection; they must, therefore, be excluded from the clinical picture of the disease under discussion. As regards pupillary signs, therefore, we are left with the single observation on the first case of a small and sluggish pupil. In addition to the clinical picture of a slow progressive polyneuritis, in itself a rarity, we have the familial incidence, the nystagmus and incoordination, the kypho-scoliosis and the mental retardation.

In their review of the literature Dejerine and Sottas were able to find only one example of the disease, a case reported by Gombault and Mallet [7], in 1889, under the title of tabes.

Case 3.—The patient was a man, aged 58, in whom the disease had apparently commenced when he was 7. There was no family history of the malady. There was flaccid paralysis and atrophy of the whole of both lower limbs, the hands and fore-arms; stocking and glove anæsthesia; loss of tendon-jerks and kypho-scoliosis. He had lost one eye and there is no mention of the pupillary reactions in the other. No note was made of hypertrophy of the nerves during life, but at the post-mortem they were recorded as slightly larger than usual. The nerve roots were found to be grossly hypertrophied, and the histological picture as described and illustrated in their paper is analogous to that of the Dejerine-Sottas case.

Cases 4 *and* 5.—In 1906, Pierre Marie presented two cases from a family of seven who were all said to be suffering from the same malady. The main symptoms were atrophy of the musculature of feet and legs, marked diminution of cutaneous sensibility, especially to touch, absence of the knee and ankle jerks and of the plantar responses, and kypho-scoliosis. The nerve trunks were thickened. Some of the subcutaneous nerves, e.g., the internal cutaneous and superficial cervicals, were unduly prominent. The pupils reacted to light but sluggishly, the speech was scanning, tremor of an intentional type was present, and all members of the family showed a slight exophthalmos.

Boveri [1] in 1910 reported Marie's cases in greater detail, together with a post-mortem report upon one of them which confirmed the pathological diagnosis. In the meantime one of the younger members of the family had developed muscular atrophy of the hands. In three the pupils were small and reacted only sluggishly to light. None had true nystagmus. One only—the eldest—had scanning speech and intentional tremor. All had some degree of sensory disturbance of the polyneuritic type, with absent deep reflexes. All showed some degree of kypho-scoliosis and exophthalmos. None had complained of lightning pains.

Boveri sought to make what appears to us a needless distinction on the basis of minor discrepancies between a Gombault-Dejerine and a Pierre Marie type of the disease, a distinction at once denied by Dejerine [2] but perpetuated by subsequent writers.

Case 6.—At the same time Boveri reported a new case from Marie's service, seen and accepted by him as such on account of the thickening of subcutaneous nerves. In this case, which was somewhat inadequately reported, there was no family history of the disease, the pupils reacted to light normally, but the main features of the disease, including the early onset and the kypho-scoliosis, were as already described. The case had previously been diagnosed as Friedreich's ataxia.

There are, however, two points worth observation in this case, the first that the patient at one stage in his illness lost the use of his hands and subsequently regained it; the second that this is the first instance in the literature in which the diagnosis is recorded without pathological verification, and it was made upon the association of a polyneuritic picture with visible and palpable hypertrophy of the peripheral nerves.

Case 7.—Long [9] in 1912 recorded a case under the title of "Atrophie musculaire progressive Type Aran-Duchenne de Nature névritique," in which there was no apparent hypertrophy of the peripheral nerves during life, nor of the nerves or nerve-roots after death; yet microscopic examination revealed an irregular but widespread hypertrophy of the sheath of Schwann, practically confined to the anterior roots between their emergence from the cord and their junction with the posterior roots. Clinically the case was one of progressive muscular atrophy commencing in the left hand at the age of 53, gradually progressive until death twelve years later, with involvement of all the musculature of the left upper limb, the right hand, and to a less extent the lower limbs; all the tendon-jerks were abolished and the plantar responses were absent. The pupils reacted normally. There were vague pains in the limbs and fibrillary twitchings, but no sensory loss.

Long admits that the absence of sensory loss in this case is a point of clinical distinction from the Dejerine-Sottas cases and other cases of this group reported up to date, but from a comprehensive review of the literature quotes other instances in which cases of progressive muscular atrophy of the "neuritic" or Charcot-Marie type and distribution have shown post-mortem hypertrophy of the sheath of Schwann (Virchow, Friedreich, Dubreuilh, Nonne, Casazza, Aoyama).

Case 8.—Schaller [14] in 1912, recorded a male, aged 20, in whom the clinical diagnosis was made upon the presence of hypertrophy of the nerve trunks of the axilla, the ulnar nerve at the bend of the elbow, the superficial branches of the cervical plexus, and the cutaneous popliteal. One of the enlarged superficial cervical nerves was excised for microscopic examination, and showed changes which are somewhat incompletely described but appear to have been characteristic. The main clinical features were a history of seven years progressive weakness, beginning in the legs and arms without any noticeable atrophy; blunting of cutaneous and deep sensibility of glove and stocking distribution; abolition of all the tendon reflexes except the triceps jerks, and partial R.D. in the weakened muscles. The pupils were normal. There was no family history of the disease, two sisters being alive and well.

Cases 9 *to* 13.—Hoffmann [8] (1912) reported five cases under the title of "Progressive Hypertrophic Neuritis," in which the diagnosis in each instance was based upon diffuse palpable hypertrophy of the peripheral nerves. The details of his third case are those of a polyneuritic picture with peripheral atrophy, sensory loss and absent tendon-jerks in a male of 20, with a progressive history from childhood. The history included tearing pains in the legs, and trunk, and paræsthesiæ of the extremities. This patient's mother (Case 4 of Hoffmann's series), aged 48, showed wasting and deformity of the feet and some wasting of the hand muscles, with absent arm-jerks and ankle-jerks, the knee-jerks being present. There was no sensory disturbance. The ulnar, median and peroneal and tibial nerves were thickened and hard. The history was that of a progressive weakness of the feet of nine years' duration.

These two cases are of particular interest, in that the mixed sensory and motor symptoms in the son were associated with purely motor symptoms in the mother. Here we have a link between the more characteristically polyneuritic form of the disease and that in which the motor functions are chiefly or, in some instances, solely affected. Hoffmann's other three cases were non-familial, began at various ages from 3 to 30, and were distinguished by progressive wasting and weakness of the extremities with occasional bouts of tearing pains and absent tendon-jerks, without paræsthesiæ or sensory loss.

Cases 14 *and* 15.—Yokomori [17] (1915) reported two cases of hypertrophic neuritis in a father and son in whom the disease did not make its appearance until adult life, beginning at the age of 44 in the father, and at 26 in the son. The clinical findings were similar in both cases, though muscular atrophy was more advanced in the case of the father who died at the age of 74, and on whom an autopsy was obtained. The initial symptoms were those of weakness and wasting of the muscles of the legs. The arms were affected much later. In both cases there was much wasting of the distal muscles of the limbs; a talipes equinus; absent knee and ankle jerks; loss of appreciation of pain and temperature below the knees and on the fore-arms and hands, and a palpable, painless thickening of the peripheral nerves, especially of the radial and ulnar. This thickening was confirmed post mortem in the one case when a similar thickening of the brachial and lumbar plexus was found. No nystagmus was observed in either case and the cranial nerves appeared normal.

Case 16.—Dide and Courjon [6] recorded a case in 1918, which was almost simultaneously recorded by Roussy and Cornil [13], having passed from one hospital to another during the war. Roussy and Cornil confirmed the diagnosis by histological examination of a fragment of one of the thickened nerves removed during life. The case is of interest in that it was non-familial; the symptoms began in adult life at the age of 40, commenced in the hands, only later affecting the lower limbs, and at the time of examination four years after the onset the disease was asymmetrical, affecting the left upper and lower limbs more than the right. Kypho-scoliosis was absent; the pupils were normal; there was no nystagmus. Intentional tremor, however, was present. The supinator and ankle-jerks were absent, the triceps-jerks present, the right knee-jerk present but the left feeble. Intermittent shooting pains had been experienced in the lower limbs, but the only sensory disturbance was in the domain of the left ulnar nerve. The spinal fluid showed 5 cells per c.mm., and a positive Wassermann reaction (the W.R. however was reported negative by

Dide and Courjon). Roussy and Cornil regarded the histological appearances in this case as a sufficient warrant of the diagnosis. They refer to Long's case as analogous. They mention also a case recorded by Chiarini and Natzari, which was distinguished by the absence of any sensory disturbance, the case clinically corresponding with the Charcot-Marie-Tooth disease. The diagnosis was determined by pathological examination.

Cases 17 *to* 21.—Dide and Courjon [5] in 1919 reported five new cases. None of these was confirmed by biopsy or autopsy, nor will the clinical details bear critical examination in comparison with the cases already reviewed. In Case 1 there was unilateral ulnar paresis with thickening of the nerve in the olecranon groove: in Case 2 atrophy of the left hand and fore-arm with thickening of median and ulnar nerves, but no sensory loss or abolition of reflexes. In Case 3 atrophy of the intrinsic muscles of the right hand was noted, with thickening of the ulnar nerve. In Case 4 there was atrophy of the upper limbs, with ape-like hands, and also of the small muscles of the feet; no loss of tendon-jerks, no sensory loss, but thickening of the median and ulnar nerves. In Case 5 there was distal wasting of upper and lower limbs, no loss of sensation or reflexes and thickening of median and ulnar nerves. Without pathological verification we feel that none of these can be accepted as an example of progressive hypertrophic polyneuritis.

Case 22.—Nattrass [12] in 1921 reported as a case of recurrent hypertrophic neuritis a boy, aged 18, seen in his third attack. The main clinical features were a subacute onset of polyneuritic symptoms with extensive paralysis, tingling in the extremities without objective sensory loss and abolition of tendon-jerks; recovery was almost complete at the end of three months. The peripheral nerve trunks were hard, enlarged and tender; no enlargement of subcutaneous nerves was observed. No pathological examination was made, and in the absence of such verification this case can hardly be accepted as a true instance of the disease under discussion, for a recurrent toxic or infective polyneuritis might well leave in its wake some thickening and tenderness of the peripheral nerve trunks.

Case 23.—Souques [15] (1926) published the case of a woman, aged 58, in whom the disease appears to have begun in childhood, first affecting the feet and, progressing very slowly. At the date of publication there were extreme atrophy and almost complete paralysis of all muscles below the knees and of the muscles of the hands. The thighs were affected but to a lesser degree. The upper limbs apart from the hands were normal. All tendon reflexes and the plantar responses were abolished. Fibrillation was seen in the affected muscles. The paralysed muscles showed no response to faradism, those less affected a partial R.D. There was slight but definite sensory disturbance peripheral distribution. The pupils were normal, there had been no lightning pains and other subjective sensory disturbance. There were no signs of cerebellar defect and no spinal deformity. The clinical diagnosis was based upon the hypertrophy of the peripheral nerves, both palpable and visible.

Cases 24 *to* 26.—Pathological reports without clinical record were also given by Marie and Bertrand (1918) [11] of two cases, and by Souques and Bertrand (1921) [16] of one case.

PATHOLOGICAL LITERATURE.

The first account of the pathology of familial hypertrophic neuritis was that of Dejerine and Sottas [3] in 1893, who obtained their material from their first published case. The autopsy on the case which Gombault and Mallet [7] had recorded four years previously had revealed a pathological picture similar to that described by Dejerine and Sottas, but Gombault and Mallet insisted in their paper on ascribing the peculiar lesions of the nerves to a sequel of the tabetic process in the spinal cord. If the clinical diagnosis of tabes in this case is questioned there can be no doubt that Gombault and Mallet were the first to describe the pathology of hypertrophic familial neuritis; they, however, failed to recognize it as a new pathological entity.

Since 1893 about nine cases of hypertrophic familial neuritis have come to autopsy of which there are records of the changes in the nervous system. In addition there have been two cases (Schaller [14], and Roussy and Cornil [13]) in which a biopsy has been performed on one of the hypertrophied nerves. The principal pathological findings have, in the main, been remarkably constant, varying only in degree.

The complete extent of the lesions and their significance have not yet, however, been accurately determined. The earlier observers laboured under the disadvantage of restricted technical methods, whilst later workers have seemed to confine their attention to the investigation of lesions by one or two of the most modern methods. For this reason, and also in view of the small number of cases reported pathologically, it appeared worth while to make as complete an examination as possible of our case of progressive hypertrophic polyneuritis.

It is here convenient to summarize the pathological changes hitherto recorded in this disease:—

(1) *The nerves.*—Pathologically the characteristic feature of the disease is the great increase in volume of the peripheral nerves. This increase in volume is greater in some nerves than in others. Marie and Bertrand [11] remarked that whereas the median nerve was relatively thin, the radial was the size of a normal sciatic. Boveri [1] found the diameter of the sciatic nerve 5 cm. below its exit from the pelvis to be 18-19 mm. Some authors have found the cranial nerves

to share in the increase in volume (e.g., Dejerine and Thomas). These authors also found that the cervical sympathetic was greatly hypertrophied.

The microscopical lesions found in the nerves can be divided into those which affect the interstitial tissue and those which are incident upon the nerve fibre itself. The former do not differ essentially from interstitial hypertrophy in other forms of neuritis. Epineurium, perineurium, and endoneurium have all been found increased in amount by various authors, though there has been some difference of opinion as to the relative increase in each of these. Dejerine and Sottas described the interstitial hypertrophy as occurring most in the perineurium; Yokomori [17] confirmed this, but Souques and Bertrand [15], on the other hand, stressed the hypertrophy of the endoneurium. But, as Marie and Bertrand point out, the great increase in volume of the nerves is due in some cases, not to the thickening in the interstitial tissue, but to an increase in tissue derived from the nervous elements.

The characteristic and outstanding lesion described in this disease is the hypertrophy and proliferation of the sheath of Schwann. Gombault and Mallet recognized this, and subsequent workers have confirmed their finding. The changes in the sheath of Schwann vary from simple hypertrophy with increase in nuclei around a single nerve fibre (Yokomori), to extensive proliferation and coalescence into masses, which may contain numbers of axis-cylinders (Marie and Bertrand), or the proliferating sheath may become flattened out into layers which appear imbricated and have been compared to the section of an onion (Dejerine and Thomas [4], Roussy and Cornil [13]; Boveri [1], Souques and Bertrand [16].) Marie and Bertrand [11] have described what they consider an intermediate stage between these two extreme forms of proliferation. In the nerves of their cases they found masses of a tissue which was multinucleated and contained many thin unmyelinated axis-cylinders. The fact that these multinucleated masses contained numbers of axis-cylinders was held by Gombault and Mallet, and later by Souques and by Roussy and Cornil, to be evidence that these bare axis-cylinders were attempts at regeneration of the nerve fibres.

Souques and Bertrand differentiate the swelling and proliferation of the sheath of Schwann from that of the interfibrillar connective tissue or sheath of Key and Retzius, which lies outside the sheath of Schwann and in apposition to it, and which is greatly hypertrophied in this disease (Souques and Bertrand, Roussy and Cornil).

In every recorded case the myelin sheaths have been few in number in the peripheral nerves, many fibres being completely devoid of myelin Dejerine and Sottas noticed that this loss of myelin was greater in the distal part of the nerve than in the proximal part. There has been more diversity of opinion about the condition of the axis-cylinders in the peripheral nerves than about any other lesion. Dejerine and Sottas found that most axis-cylinders had disappeared. Souques and Bertrand observed some degeneration of the axis-cylinders with fragmentation, the fragments often ending in an arborization which was strongly argentophil. Marie and Bertrand came to the conclusion that although some axis-cylinders were swollen and others appeared rather thin, they were, in general, well preserved. Yokomori decided that the axis-cylinders were relatively normal in the neighbourhood of the spinal cord, but very scanty peripherally, with occasional swellings in part of their course. They might even disappear completely toward the end of the nerves.

(2) *The nerve roots and cauda equina.*—Gombault and Mallet, Dejerine and Sottas, Souques and Bertrand and Dejerine and Thomas in both their cases described an appreciable macroscopic thickening of the cauda equina, but to Boveri and to Yokomori the cauda equina appeared normal. Neither did these two authors find the nerve roots hypertrophied. The other writers quoted above found a thickening of both anterior and posterior roots. The lesions in the roots were similar to those in the peripheral nerves, but more intense (Marie and Bertrand, Dejerine and Thomas), especially the demyelination (Dejerine and Sottas, Gombault and Mallet), and the formation of "onion bulb" masses (Marie and Bertrand). Dejerine and Sottas found these changes most extensive in the anterior roots of the cauda equina.

(3) *The spinal ganglia.*—The lesions of the spinal ganglia have been studied especially by Marie and Bertrand and Souques and Bertrand.

Marie and Bertrand detected many signs of degeneration in the ganglion cells. In some the nucleus had entirely disappeared, in others the neurofibrils had disappeared from part of the cell body, whilst in others the cell had taken on a pseudo-amœboid form. Around most of the nerve cells there was an increase in satellite corpuscles. No mention is made of the presence of any masses of tissue derived from the sheath of Schwann or capsule cells in the ganglia.

Souques and Bertrand noted changes only in the lumbar and sacral ganglia, the dorsal and cervical appearing normal, though the latter were macroscopically hypertrophied. These authors mention multiplication of the capsular nuclei and hypertrophy of the extracapsular layers of cells. They also describe various stages of degeneration of the ganglion cells, up to the final stage of a mass of amorphous cellular tissue surrounded by satellite corpuscles. The ganglion cells, although most of them showed degenerative changes, were normal in number. Dejerine and Thomas [4] in their second case reported a decrease in the number of ganglion cells, with atrophy of those remaining, and hyaline degeneration of the blood-vessels. Gombault and Mallet observed interstitial changes in the ganglia similar to those occurring in the roots, but normal ganglion cells.

(4) *The spinal cord.*—Degeneration of the posterior columns of the spinal cord has been described in all the recorded cases of this disease, and is considered to be a sequel to the pathological process in the nerves. Dejerine and Sottas first noticed that the degeneration was most severe and extensive in the lumbo-sacral region. In the dorsal and cervical regions the column of Goll only was affected, the column of Burdach escaping. This was confirmed by Dejerine and Thomas, Souques and Bertrand, and Marie and Bertrand, though Boveri and Yokomori found that the degeneration was present only in the inner part of the column of Goll throughout the cord. In Boveri's case the crossed pyramidal tracts, the direct cerebellar and the direct pyramidal tracts also appeared pale when stained by the Weigert-Pal method, but Boveri himself suggested that this apparent degeneration was due to an error in technique.

Marie and Bertrand and Souques and Bertrand traced the degeneration of the posterior columns up as far as the nucleus gracilis in the medulla. No lesions have been discovered above this level. Yokomori has described an increase in neuroglial tissue in the posterior columns of the cord. Other writers make no mention of neuroglial reaction.

There has been some difference of opinion as to the condition of the anterior horn-cells in the spinal cord. Dejerine and Thomas described atrophy of a certain number of them, but considered that most were normal. Boveri also observed atrophy of the cells, but was not completely satisfied with his methods of examination. Yokomori found that they were much diminished in number, whilst those remaining were atrophied, especially in the dorsal region; though the neurofibrils running through them appeared to be thickened. Souques and Bertrand also described a diminution in the number of anterior horn-cells, many of which exhibited all the signs of an acute cytolysis.

(5) *The muscles.*—All observers agree that in muscles atrophied

during life a simple atrophy is found histologically. In addition, Dejerine and Sottas and Dejerine and Thomas noted a thickening of the blood-vessels, whilst Marie and Bertrand interpreted the changes in the blood-vessels as a mesarteritis rather than as an endarteritis or periarteritis. These authors, and also Gombault and Mallet, Boveri, Dejerine and Thomas and Yokomori, reported an increase in interstitial fat in the muscles.

The essential lesions of progressive hypertrophic polyneuritis would therefore appear to be:—

(1) A hypertrophy of the peripheral nerves, ganglia, and spinal roots, depending on two factors—one an increase in the interstitial tissue; the other, which is peculiar to the disease, a proliferation of the cells of the sheath of Schwann, with a concomitant demyelination of nerve-fibres.

(2) An associated degeneration of the posterior columns of the spinal cord, the relation of which to the lesions in the nerves and nerve-roots may be consecutive, though this has not yet been definitely decided.

CLINICAL HISTORY OF THE CASE.

C. H., aged 52, carpenter, was admitted into Guy's Hospital under Dr. J. J. Conybeare, on September 15, 1927. He complained of pains and numbness in his arms and legs, diarrhœa and attacks of faintness with loss of consciousness.

The illness had commenced three years previous to admission, and the first symptoms were pains in the arms, which worried him particularly at night while in bed; and dulness of sensation in the hands, the latter chiefly in the mornings. He next began to lose energy and appetite, and gradually became weaker, so that he was obliged to give up his work. Later he began to suffer with stabbing pains in his legs; these were like exaggerated pins and needles, felt chiefly in the calves and in the soles of his feet. These pains also came on chiefly at night and disturbed his sleep. By about August, 1926, diarrhœa became a troublesome symptom. He would pass on the average two or three watery motions in the twenty-four hours, and sometimes the bowels would act without his being aware of it. He stated that he had suffered from momentary lapses of consciousness, which would come without warning at any time; they would last only a few seconds. On one or two occasions he had fallen, but had never hurt himself. He had never passed urine in any of these attacks. He did not feel dazed after an attack.

He could give no history of any previous illness, except pneumonia as a child, and influenza several times. He had never had syphilis.

Family history.—He was married and had two living healthy children. Two brothers died from complaints similar to his own: he was emphatic that his brothers had suffered in precisely the same manner as himself and that in each case death had taken place three years after the onset of symptoms.

Dr. Charles Ham, who had been the family doctor for many years, very kindly wrote a letter, in reply to inquiry which, in view of the many details which it contains, we quote in full.

> "I will be only too glad to give you the history as far as I know it of the varied members of the H. family, and if you find anything further in your investigations, I should be glad if you would let me know.
>
> The father died of tubercle, the mother of old age. One sister died of asthma and tubercle. The diagnosis in these cases was quite definite. One sister, about 55, is alive and fairly well.
>
> The following three (a sister and two brothers, all dead) presented great difficulties in diagnosis and in fact they were not really diagnosed at all.
>
> The sister, whom I saw a short time before she died, was suffering with acute diarrhœa, the heart was dilated, and there was a trace of albumen in the urine. At the time I did not realize the nature of the case, but getting the history after her death from the sister I think she must have suffered in the same way as the brothers.
>
> The symptoms in the two brothers I attended were very similar, and to save time I will describe them together. First, they complained of tiredness in legs and lack of sleep, then shooting pains developed in the legs which were very severe, and symptoms exactly like a peripheral neuritis developed. There was no evidence of alcohol or arsenic, but the teeth were very septic and there was also a marked growth of streptococci in fæces. The urine was quite normal. Nothing else of an abnormal nature was found. The teeth were extracted, but no change in symptoms followed.
>
> The patient gradually got worse, the pain more marked, and the legs became very thin. The heart, lungs, and other organs were apparently healthy. This state of affairs went on for several months; then vomiting set in, and profuse diarrhœa—very offensive and with practically no control; both these symptoms continued on and off right to the end. Other symptoms were emaciation, frequent attacks of unconsciousness lasting from one to four or five minutes, great depression, great distaste for food and very little saliva. The legs remained the same—often a great deal of pain. Towards the end the heart became dilated and a trace of albumen appeared in the urine. X-rays showed nothing.
>
> Both brothers had absence of acid in stomach contents. The fæces gave an abundant growth of Gaertner's bacillus. One brother had signs of pancreatic deficiency.
>
> I understand a post-mortem examination was done on the patient who died in King's College Hospital. They told me nothing was found abnormal except a little fluid in the chest.
>
> I could not get an autopsy on the second brother."

Dr. C. E. Newman, of King's College Hospital, kindly furnished the following extract from the notes on the case of the youngest brother, who died in that hospital at the age of 52:—

> "E. H. was in this hospital from 29.12.22 to 16.1.23. He had chronic colitis and neurasthenic symptoms, but with a true peripheral neuritis in the legs. There was excess of streptococci in the fæces. He died suddenly of œdema of the lungs. At the post-mortem examination the heart was absolutely normal, the lungs were œdematous but the changes were acute only. The brain was normal. There were patches of degeneration and replacement fibrosis in the zona fasciculata of the suprarenals and of the sympathetic ganglia; also patches of replacement fibrosis in the femoral and external popliteal nerves. He had œdema and trophic changes in the skin of both feet."

Condition on admission.—The patient looked wasted, particularly in the lower extremities. He had been bedridden for some months and was unable to stand upright without support. In describing his condition he explained that the legs and feet were anæsthetic to light touch, heat and cold, but at the same time he suffered with burning pains on the soles of his feet.

Cardiovascular symptoms: The apex beat could not be felt; the heart sounds were extremely feeble, but no murmurs were heard. Systolic blood-pressure was 95 mm., diastolic 60 mm., hæmoglobin 72 per cent., white cells 9,500 per c.mm., red cells 4,200,000 per c.mm. The differential count normal. The blood Wassermann was negative.

Alimentary system: His tongue moist and clean. All teeth had been extracted some years before for pyorrhœa alveolaris. No pigmentation was present in the mouth. The liver and spleen were not palpable.

Chemical examination of fæces: "Acid to litmus; slight excess of fatty crystals; some fat globules and striated meat fibres. No lack of stercobilin. No hæmatoporphyrin; guaiac negative."

Bacteriological examination of fæces: "Cultures gave a mixed growth of *Bacillus coli communis* and *B. lactis aerogenes*.

Fractional test meal: Marked hypochlorhydria with some free hydrochloric acid at the end of two hours.

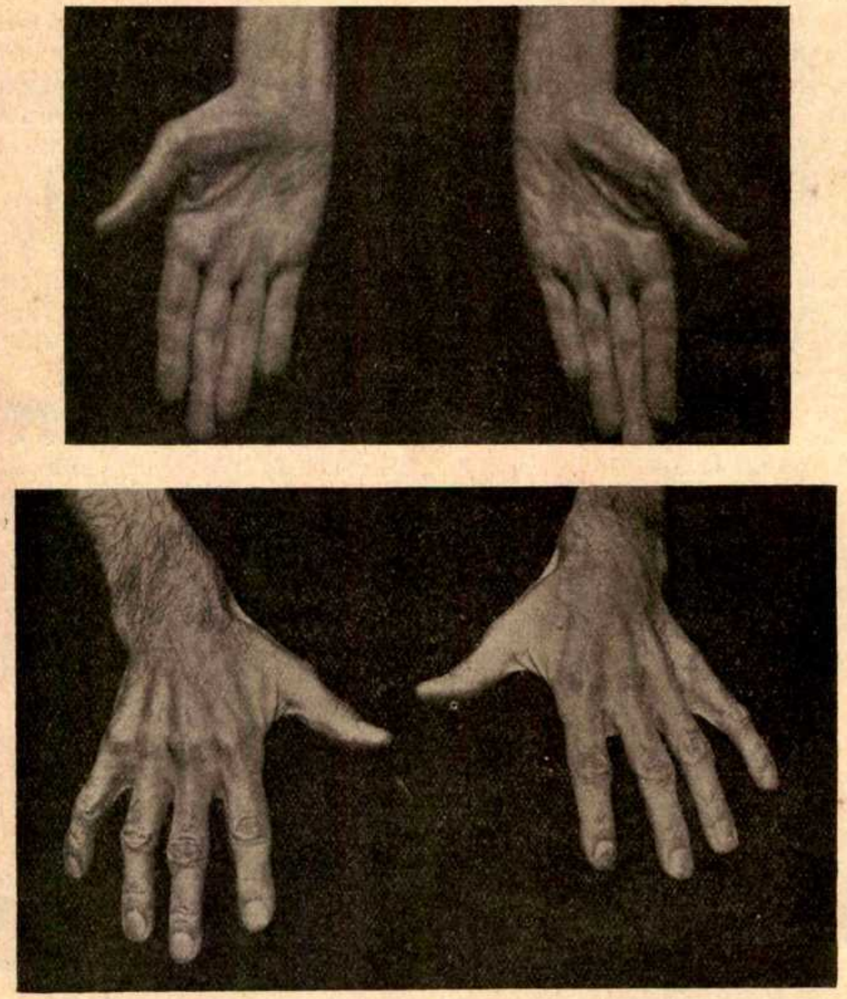
An alimentary X-ray showed no abnormality. The urine was normal, and there was no disturbance in the respiratory system.

Central nervous system: Intelligence was normal and he appeared to have a good memory. There was no speech defect. The visual fields were normal and the optic discs showed no abnormality.

A watch was heard at 3 ft. on either side. The pupils were small and the right was a little irregular in outline. Both reacted in accommodation but the reaction to light was sluggish, particularly of the right. The ocular movements were full and normal, and there was no nystagmus. The functions of the remaining cranial nerves were unaffected.

Sensation was normal on the head, palate, trunk and upper extremities. On the lower limbs there was loss of tactile discrimination below the knees.

Sensibility to pinprick was diminished over both legs to about 3 in. above the knees. To cotton wool he was anæsthetic over the feet and on the front of the legs. He was unable to distinguish between heat and cold on the feet and legs. Deep pressure on the muscles caused some discomfort. Vibration sense was within normal limits, and the sense of position in the joints was not impaired except in the big toes. He was unsteady in the Romberg attitude, but his legs were so weak that they could scarcely support the weight of his body.



FIGS. 1 and 2.—Hands of patient C. H., showing wasting of intrinsic muscles.

There was marked general muscular wasting, but the following groups were especially affected: The intrinsic muscles of the hands, including the thenar and hypothenar eminences; the flexors of the wrist and fingers, especially on the left; the quadriceps femoris, anterior tibials and intrinsic muscles of the feet. The hand grips were weak. The other muscles of upper limbs and the musculature of the trunk were relatively normal. The extensors of the knees were weak and he was unable to stand unsupported. Dorsiflexion and plantar flexion at the ankles were feeble. There was no power of voluntary movement in the toes. Coarse fibrillary twitching was occasionally observed in the quadriceps of both sides.

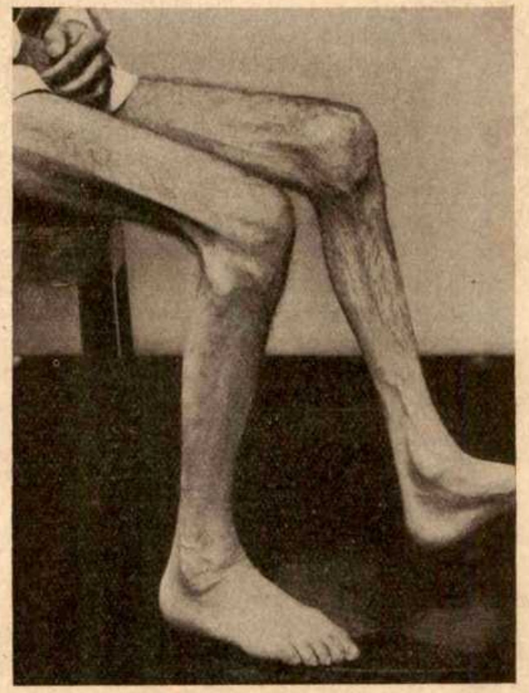


FIG. 3.—Lower limbs of patient C. H. showing generalized muscular wasting especially below the knees. The left foot is passively supported.

The electrical reactions of the leg muscles were poor in quality owing to wasting, and there was partial reaction of degeneration as they responded to faradism and gave a slow response to galvanism. The thigh muscles gave better contractions and the reactions were normal, i.e., good response to faradism and brisk contractions with galvanism. The muscles of the upper limbs were not tested.

Some of the peripheral nerves, viz., the ulnars, anterior crurals and external popliteals, were easily palpable but not tender. Above the left clavicle there was some abnormal fulness due to the thickened cords of the brachial plexus.

X-ray examination showed that there was no cervical rib present.

PATHOLOGICAL EXAMINATION.

The case came to autopsy on December 1, 1927. There was found considerable atrophy of the muscles of all four limbs, more noticeable distally than centrally.

All the accessible peripheral nerves could be easily palpated. On dissection all the nerves were somewhat larger than normal, but their chief abnormality lay in their excessive firmness. The enlargement of the nerve-trunks seemed to be rather greater close to the ganglia, and there was little diminution in size as one passed peripherally from the ganglia. The nerves proximal to the ganglia did not appear to be much enlarged. The ganglia, on the other hand, were greatly increased in size in the cervical, upper dorsal and lumbo-sacral regions. The upper level of the enlargement of the ganglia was at the sixth cervical, the fifth cervical being small on both sides. There was a distinct difference between the size of the ganglia on the two sides in the cervical and upper dorsal region, the eighth cervical and first dorsal being very much larger on the left than on the right side.

On cross-section of the peripheral nerves it was impossible to see the individual fibres. The nerve appeared homogeneous and resembled a tendon.

Exact measurements of two nerves were made: The musculo-spiral nerve at a distance of 20 cm. from the cord measured 8 by 4 mm. The median nerve at the same distance measured 6 by 4 mm. The diameter of the sciatic nerve throughout its extent appeared to be at least twice the normal. The cranial nerves did not seem to be increased in size. The cauda equina, however, was considerably thickened.

MICROSCOPICAL EXAMINATION.

The peripheral nerves.—Sections of the brachial plexus and of the musculo-spiral, ulnar, and internal cutaneous nerves of the arm were taken at definite measured distances from the spinal cord, 15 and 35 cm. in the case of the nerves of the arm. The sciatic nerve was sectioned in the gluteal region, in the thigh and in the popliteal space. The staining methods employed were those of Weigert-Pal with carmine counterstain, Bielschowsky, Mallory's anilin blue-orange G. (modified), Scharlach R., and iron hæmatoxylin with van Gieson's counterstain and the same stain with an eosin counterstain. The same methods were used for staining the spinal ganglia.

It was in sections stained with hæmatoxylin and van Gieson's counterstain that the characteristic lesion was seen most clearly. Nearly all the nerve-fibres appeared swollen and had an excess of nuclei. In between the nerve-fibres and separating them from one another lay masses of a non-nucleated, homogeneous substance which stained deep yellow with the van Gieson counterstain. These masses for the most part lay irregularly distributed in the nerve-bundle, but in some nerves, especially in the most distal portion of the sciatic they seemed to be collected in a more regular fashion as a layer directly under the capsule of the nerve-bundle. As regards the distribution of these masses in the various portions of the nerves examined, we found that they were more

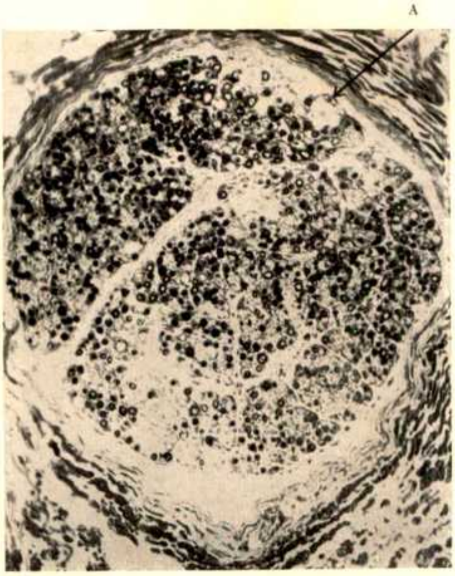


FIG. 4.—Transverse section of median nerve stained by the Weigert-Pal method showing a plasmatic swelling directly under the capsule of the nerve bundle, A. Some nerve fibres appear swollen. There are some demyelinated fibres present, but myelination is relatively good as the section was taken from a high level in the nerve. The interstitial tissue is increased.

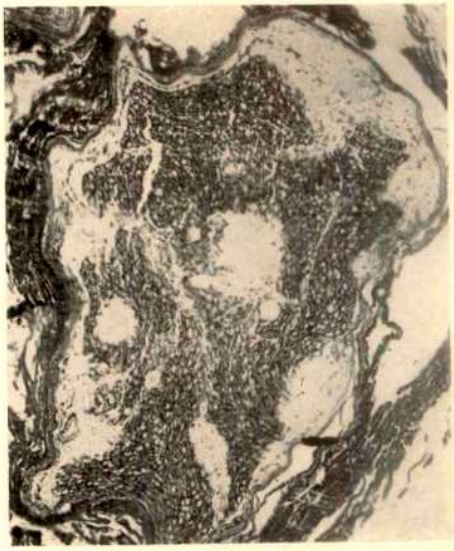


FIG. 5.—Transverse section of sciatic nerve stained with hæmatoxylin and van Gieson. The shape of the nerve bundle is grossly irregular and there is much interstitial fibrosis. There are many plasmatic swellings present, some rounded and some irregular in shape. They tend to be collected around the periphery under the capsule, although some are irregularly distributed in the interior of the bundle.

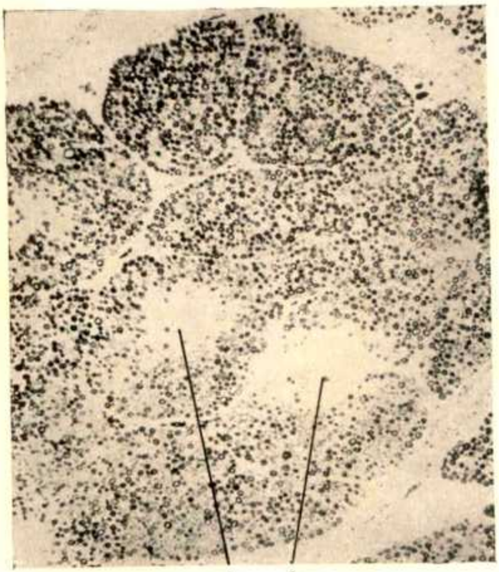


FIG. 6.—Transverse section of cauda equina stained by the Weigert-Pal method. Two large plasmatic swellings are to be seen in the middle of the field, A. Many nerve fibres in one half of the field are poorly myelinated.

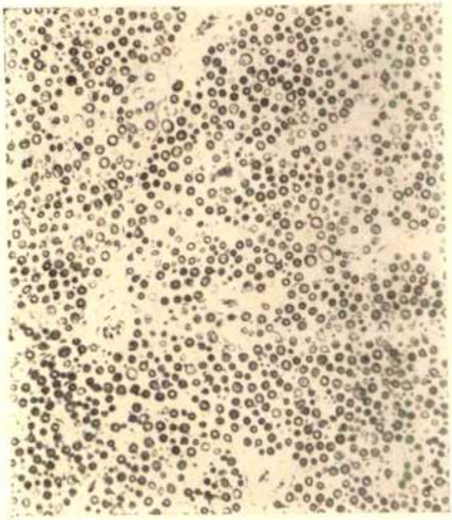


FIG. 7.—Transverse section of cauda equina at a higher level than Fig. 3, stained by the Weigert-Pal method. The nerve fibres are more widely separated than normal by fibrous tissue and there is much thickening around blood-vessels. Some nerve fibres appear swollen.

To illustrate Dr. R. S. de Bruyn's and Dr. Ruby O. Stern's paper.

numerous in the proximal portions of the nerves, whereas degeneration of myelin was more evident in the distal portions. The origin of these masses would seem to be an hypertrophy of the sheaths of Schwann, although no definite intermediate stages between the swollen sheath around a single nerve-fibre and these non-nucleated masses could be determined. We can only assume that these masses are formed of swollen sheaths of Schwann which have coalesced and in which the axis-cylinders, myelin sheaths and nuclei have all degenerated, since we could nowhere find traces of degenerating nuclei, myelin sheaths or axis-cylinders in the masses. Very occasionally a thin axis-cylinder might be seen in the periphery of a mass, but not more often than was a blood-vessel. Boveri described similar masses of a homogeneous tissue, which stained deep red with eosin, in the peripheral nerves. The masses which we have found also stained red with eosin and would appear to be identical with those observed by Boveri. He gave no opinion as to their origin. Careful search for the "onion bulb," laminated masses regarded by the majority of writers as the characteristic lesion in the peripheral nerves failed to reveal them. Nowhere could we find any suggestion of either a laminated or a nucleated mass. We have felt it necessary to give a name to the homogeneous tissue which we have found present constantly in the peripheral nerves, and also, as will be seen later, in the ganglia. To obviate any possible objections to the use of a descriptive term, assuming the tissue to have a certain mode of origin, we propose to call the substance of which the masses are composed "plasmatic substance," which is descriptive only in that it assumes the mass to contain protoplasm. We have called the masses of tissue "plasmatic swellings."

Bielschowsky preparations demonstrated these plasmatic swellings well. They appeared somewhat argentophil, though not so strongly as the axis-cylinders, none of which could be seen to enter the swellings. Axis-cylinders were either pushed to one side and ran around the plasmatic swellings, or they became broken off at the edge of the swellings, where they formed small, terminal, strongly argentophil bulbs. Apart from these interruptions the axis-cylinders seemed relatively normal. They were certainly not increased in number. In a few fibres they appeared rather thin and occasionally small bulbous swellings could be seen on them. The Bielschowsky method also showed very plainly the hypertrophy of the interfibrillar reticular tissue or sheath of Key and Retzius. The wavy fibres of this sheath could be seen surrounding the plasmatic swellings, but never transversing them. These fibres were sometimes a little difficult to distinguish from the axis-cylinders, though usually the latter were easily distinguished by their straighter course and thicker diameter.

In sections stained by the Weigert-Pal method the plasmatic swellings appeared as colourless areas which did not take the carmine counterstain, and in which no trace of myelinated material could be made out. Many fibres were seen to have lost their myelin sheaths and, as we have previously mentioned, this was particularly evident in the distal portions of the nerves.

In the median nerve, for example, at a distance of 15 cm. from the spinal cord myelination was almost normal, but 35 cm. from the cord a large number of demyelinated fibres were present.

In Scharlach R. preparations the plasmatic swellings did not stain, but in several of them minute droplets of orange-red, fat-staining material were to be seen. No droplets of fat could be seen in the nerve fibres.

By the anilin blue-orange G. method the plasmatic swellings stained a deep blue, quite distinct from the paler blue of the interstitial collagenous tissue.

Changes in the interstitial tissue were seen to the greatest extent in the sciatic nerve. In this nerve all the connective tissue coats of the nerve-fibre were greatly thickened, but the perineurium appeared to be the most affected. The chief thickening of the whole nerve was, in the sciatic, due not to the presence of the plasmatic swellings, although numbers of these were present, but to the large amount of interstitial tissue between the nerve bundles. The nerve bundles themselves were grossly irregular in shape. This irregularity was probably caused partly by the shrinkage of the nerve bundles and partly by the irregular distribution of the interstitial tissue. The blood-vessels in the nerves were thicker than normal, the adventitia especially being hypertrophied.

The spinal ganglia.—Sections were taken from the lower cervical and upper dorsal ganglia, and from the fifth lumbar and first sacral ganglia. Similar lesions to those in the peripheral nerves were found in the ganglia, although the interstitial changes were not so intense. Plasmatic swellings were found in all the ganglia. They occurred in two distinct positions: (1) in between the nerve fibres, where they could be seen forming globular or oval masses resembling those in the peripheral nerves; and (2) in relation to the ganglion cells. Here they appeared to arise within the capsule cell layer, and various stages in their formation from these cells could be made out. The earliest stage seemed to be a swelling of the capsule cells with multiplication of their nuclei. In a large number of cells the process was arrested at this stage and the condition therefore approximated to that described by Souques and Bertrand. In other cells, however, the cells became more swollen, and in their cytoplasm there appeared a mass of homogeneous material, staining deep yellow with van Gieson, which was identical with the plasmatic substance. The nuclei disappeared at this stage, and in the next stage the cells became so distended that their walls collapsed and adjacent cells coalesced, forming a large plasmatic swelling. These swellings often indented the external limiting membrane of the ganglion cells, but could nowhere be observed to penetrate into the ganglion cells, although the cytoplasm of these cells appeared distorted as if pressed upon by the plasmatic swelling.

We were able to confirm the degenerative changes in the ganglion cells that have been so frequently recorded. Some cells had undergone such extreme atrophy that they were distinguished from adjacent plasmatic swellings only by their staining reactions with van Gieson's counterstain, or with the

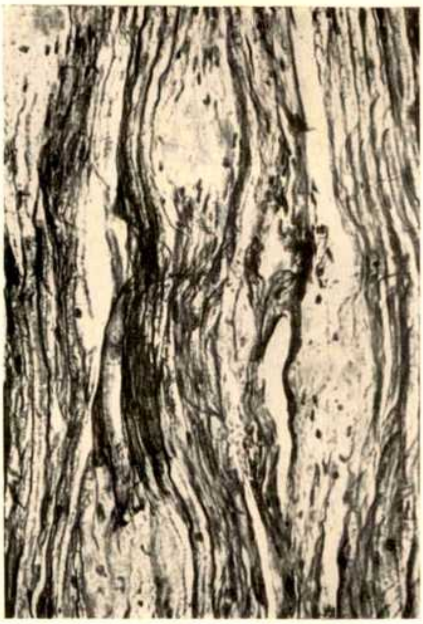


FIG. 8.—Longitudinal section of the left first dorsal root ganglion stained with hæmatoxylin and van Gieson, showing plasmatic swellings among the nerve fibres resembling those in the peripheral nerves.

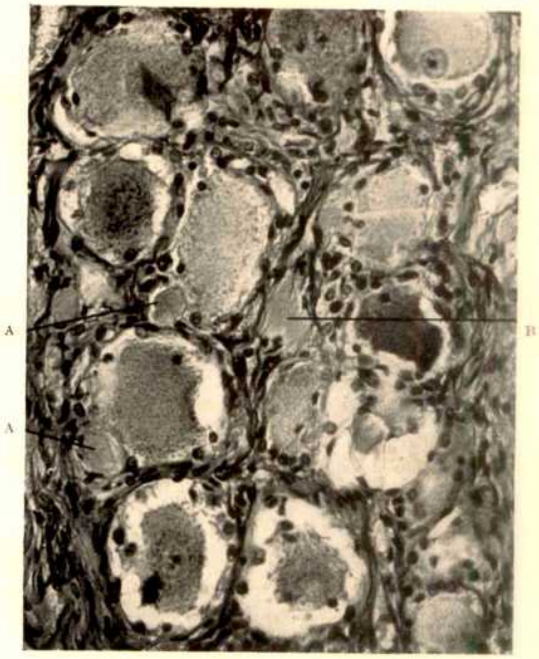


FIG. 9.—Longitudinal section of the right first dorsal ganglion stained with hæmatoxylin and van Gieson. Several rounded plasmatic swellings are to be seen in relation to the ganglion cells A, and others are present in between the nerve fibres B. Most of the ganglion cells are distorted in shape and have eccentric nuclei, and many are shrunken away from their capsules.

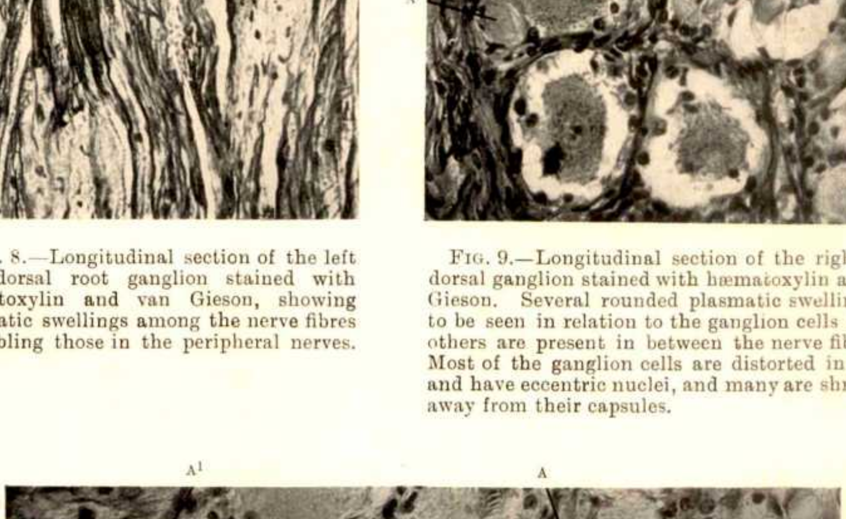


FIG. 10.—Longitudinal section of the right first dorsal ganglion stained with hæmatoxylin and van Gieson, showing plasmatic swellings in relation to the ganglion cells. Three adjacent swellings are to be seen arising in the capsule cell layer of one ganglion cell A. There is hypertrophy of the capsular cells of other ganglion cells with plasmatic swellings A^1 in relation to them and an increase in the amount of interstitial tissue. One ganglion cell containing an excess of melanin pigment has become shrunken away from the capsule cell layer. Some plasmatic swellings between nerve fibres are also seen, B.

anilin blue-orange G. stain. Others showed slighter degrees of degeneration. Many cells were seen with irregular outlines, and in several the external membrane had become infolded. Eccentric nuclei and distorted nuclear shapes were amongst the commoner signs of degeneration observed. In addition, many cells contained an excess of melanin pigment in their cytoplasm. This was noted especially in the first dorsal ganglion. There was an increase in the number of capsule cells around most of the ganglion cells, and in the first sacral ganglion the interstitial tissue was also increased. Myelination was good in the ganglia on the whole, though in each ganglion a few demyelinated fibres could be seen, the position of which was quite independent of the plasmatic swellings.

Nerve roots and cauda equina.—The majority of nerve roots were well myelinated. In a few, the early formation of a plasmatic swelling could be made out as a small, non-nucleated, homogeneous mass which gave the characteristic staining reactions of the plasmatic swellings, lying in between the nerve fibres. The nerve fibres themselves were somewhat swollen, but appeared relatively normal compared with the fibres of the peripheral nerves. There was a slight increase in the interstitial tissue.

The cauda equina showed much more extensive lesions than the other nerve roots. The interstitial fibrosis was particularly striking in some of the bundles of fibres, whilst a large number of fibres were devoid of myelin. There was a copious formation of plasmatic substance, which, even more than in the peripheral nerves, tended to be distributed just under the capsule of the nerve bundles.

Spinal cord.—Only in the sacro-coccygeal region could any very definite degeneration of the posterior columns be found. Otherwise, throughout the cord the posterior columns appear only slightly, if at all, paler than the other tracts when stained by the Weigert-Pal method. In sections stained by the Nissl method the anterior horn cells were for the most part normal in number, size and shape, but in the cervical and lumbo-sacral enlargements a few cells in the lateral group displayed signs of central chromatolysis with eccentric nuclei. As these lateral columns of cells supply the long nerves to the limbs, the affected cells probably corresponded to the nerve fibres in which degenerative changes were most evident.

Bielschowsky preparations showed that the neurofibrils passing through the cells were normal. No cellular infiltration of the cord and no excess of neuroglial tissue could be determined.

Sections of the medulla, pons, mid-brain and cerebral cortex all appeared normal.

Muscles.—Portions of the biceps brachialis and gastrocnemius were embedded in celloidin, stained by iron hæmatoxylin and counterstained with van Gieson. In sections of muscle stained in this way the picture was one of irregular atrophy. Most muscle fibres were of fair size, but very small fibres were also present. The largest observed measured just over $80\,\mu$, the smallest having only their bare nuclei visible. The majority of the fibres were rounded, whilst a few contained vacuoles in their cytoplasm. No fat replacement or other interstitial change was noted, and the condition was obviously one of "simple atrophy," due to nerve lesion. The vessels were slightly thickened. The nerves in the muscles proved of interest, as in between the nerve fibres were to be seen masses of tissue giving similar staining reactions to, and resembling in their structure, the plasmatic swellings in the peripheral nerves. They were usually found under the capsule of the nerve bundle and in some instances they appeared to be centred on a blood-vessel. Most of the nerve fibres were poorly myelinated as though affected by a lesion at a higher level in the nerve.

DISCUSSION.

Clinically, the case we have recorded corresponds pretty nearly with the original description of Dejerine and Sottas. Our patient, as theirs, presented a polyneuritic symptom picture with wasting, weakness, and sensory loss of peripheral distribution. In both, the pupils were small and reacted sluggishly to light (the Argyll-Robertson pupils observed in their second case must be disregarded for the reasons already given). Coarse fibrillation and partial R.D. were common to both. In both a history of lancinating pains was obtained. In both a striking family history of the disease was present. Certain features present in the Dejerine-Sottas cases, namely kypho-scoliosis, nystagmus and incoordination of the upper limbs, were absent in our own. On the other hand, the history of the disease in our patient differs in the most striking manner from that of the Dejerine-Sottas cases and from all others since described. Our patient died within three years of the onset of his malady, as did his two brothers and one sister who appear also to have been affected by it. Severe diarrhœa was an early and persistent symptom in all the cases of this family; in our case the test meal showed marked hypochlorhydria, and in the other members of the family also there appears to have been a deficiency of acid in the gastric juice.

On the pathological side this case conforms in some respects to those which have already been described. The hypertrophy of the peripheral nerves, due in part to thickening of the interstitial tissue, and in part to the new formation of masses of tissue derived from the sheath of Schwann, the amount of demyelination in the nerve fibres and the changes in the cells of the spinal ganglia resemble the classical pathological picture. But there are several points of difference in our case. The presence of masses of non-nucleated tissue, however derived, in relation to the capsule cells of the ganglia, has not hitherto been recorded; neither could we find any reference to the condition of the nerve fibres in the muscles. Apart from these additions to the histological study of the disease, there are certain differences in our observations which seem to point to the fact that this case may have been of a slightly different pathological type from those previously described. The complete absence of the "onion bulb" masses in the peripheral nerves, which other writers have considered a characteristic feature of the disease, and their replacement by definite non-nucleated, homogeneous masses, varying in size, and derived apparently from hypertrophied cells of the sheath of Schwann, would suggest that in our case either a slightly different process affected the peripheral nervous system, or that we have observed a different stage in the same morbid process.

The absence of any marked degeneration in the dorsal columns may be due to the relatively short history of the case and to the early nature of the disease in the dorsal nerve roots and ganglia. At the same time the absence of "onion bulb" formations and the curious plasmatic swellings found in the nerves seem to constitute qualitative differences between the pathological process in this case and that found in the majority of cases previously recorded.

SUMMARY AND CONCLUSIONS.

(1) The original paper in which Dejerine and Sottas reported two cases of the disease, which they were the first to name hypertrophic neuritis, has been summarized in some detail.

(2) These two cases were brother and sister, but in view of an isolated case already reported by Gombault and Mallet (under the title of tabes) Dejerine and Sottas did not regard the malady as essentially familial.

(3) The clinical picture described in the cases of Dejerine and Sottas was that of a slowly progressive polyneuritis with both motor and sensory symptoms.

(4) The pupils were small in both their cases. In one case they were Argyll-Robertson. This patient, however, was known to have had syphilis six years previously. This point, which appears to have escaped the notice of most subsequent writers on the subject, is of particular significance since this is the only case we can discover in the literature in which the Argyll-Robertson pupil was observed. The miosis observed in this and other cases, including our own, is almost certainly due to an extension of the disease to the cervical sympathetic fibres in the first thoracic roots.

(5) In Dejerine and Sottas' first case no hypertrophy of the peripheral nerves or nerve trunks was noted during life. When this was

discovered post-mortem the surviving patient was re-examined with especial attention to the point, and it was noted for the first time that all the palpable nerves were increased in volume.

(6) Thus of two signs which have come to be regarded in some of the modern textbooks as characteristic of the malady, one, the Argyll-Robertson pupil, is shown to have no value; the other, hypertrophy of the accessible nerves, may be inconspicuous, and may be observed only if especially looked for.

(7) A critical review of the cases subsequently reported, based primarily upon those in which the diagnosis has been confirmed by pathological examination, shows that the polyneuritic picture may vary in type and distribution. Thus the upper or lower limbs may be in different cases more, or less, severely affected, and whilst as a rule sensory and motor symptoms develop *pari passu*, the one group may precede or overshadow the other.

(8) In addition to the polyneuritic signs, certain others, such as kyphosis, nystagmus and motor inco-ordination, were observed by Dejerine and Sottas in their two original cases and are recorded in a certain number of those subsequently reported.

(9) The age of onset in nine of the fourteen cases in which this point was ascertained was under 21 years. In the remaining five the disease began at the ages of 26, 39, 40, 44 and 50.

(10) A familial history is recorded in four pairs of cases out of a total number of seventeen cases which we have accepted as genuine examples of the disease.

(11) The course of the disease has in all cases previously recorded been slowly progressive, and death has occurred from intercurrent disease.

(12) The case which we record is that of a male whose symptoms began at the age of 49. The polyneuritic symptoms progressed rapidly and were associated with severe and intractable diarrhœa. The patient died three years after the onset of his illness. From the information given by the family physician it appears that one sister and two brothers of the patient died with a similar disease.

(13) The outstanding clinical features of the case were the signs of a severe polyneuritis, both motor and sensory, with major involvement of the lower limbs. The pupils were small but reacted sluggishly to light. The cords of the brachial plexus and the peripheral nerves were easily palpable and thought by some observers to be thickened.

(14) The pathological changes were mainly incident upon the peri-

pheral nerves and spinal ganglia. The degeneration of the posterior columns of the spinal cord described in every case hitherto reported, was almost completely absent in our case. In the peripheral nerves both interstitial and neural elements were hypertrophied. In the distal portions of the nerves there was much loss of myelin.

(15) The characteristic feature of the disease process in the nerves was the presence of masses of non-nucleated tissue which appeared to arise from the sheath of Schwann and, fusing, formed larger masses.

(16) Earlier stages in the formation of these masses were seen in the spinal ganglia both in relation to the capsules of the ganglion cells and to the nerve fibres, and also in the fine intramuscular nerves.

(17) The appearance of these non-nucleated masses does not correspond with any pathological appearances in the peripheral nerves hitherto described in this disease and may represent an earlier stage or possibly a slightly different process.

We wish to acknowledge our indebtedness to Dr. J. J. Conybeare for permission to publish the case and enabling us to obtain the post-mortem examination; to Dr. C. P. Symonds, who suggested the true diagnosis at the bedside and has helped us in reviewing the clinical literature; to Mr. J. W. Shackle for a translation of Hoffmann's paper; also to Dr. Charles E. Ham, for providing us with the family history, and to Dr. C. E. Newman for notes of the brother who was a patient in King's College Hospital.

To Dr. J. Godwin Greenfield we wish to express our gratitude for his interest in the pathological investigation of the case and for his valuable advice on the interpretation of the pathological findings.

REFERENCES.

[1] Boveri, P. *Semaine Méd.*, 1910, **30**, 145.
[2] Dejerine, J. *Rev. Neurol.*, 1906, **14**, 558.
[3] Dejerine, J., et Sottas, J. *Comp. rend. de la Soc. de Biol.*, 1893, **5**, 63.
[4] Dejerine, J., et Thomas, A. *Nouv. Icon. de la Salpêtr.*, 1906, **19**, 477.
[5] Dide, M., et Courjon, R. *Rev. Neurol.*, 1919, **35**, 825.
[6] *Idem., idem.* *Nouv. Icon. de la Salpêtr.*, 1916-1918, **28**, 377.
[7] Gombault, A., et Mallet. *Arch. de Méd. Expér.*, 1889, **1**, 385.
[8] Hoffmann, J. *Zeitschr. f. Nervenheilk.*, 1912, **44**, 65.
[9] Long, Ed. *Nouv. Icon. de la Salpêtr.*, 1912, **25**, 281.
[10] Marie, P. *Rev. Neurol.*, 1906, **14**, 557.
[11] Marie, P., et Bertrand, I. *Ann. de Med.*, 1918, **5**, 209.
[12] Nattrass, F. J. *Journ. Neurol. and Psychopathol.*, 1921, **2**, 159.
[13] Roussy, G., et Cornil, L. *Ann. de Méd.*, 1919, **6**, 296.
[14] Schaller, W. F. *Arch. Int. Med.*, 1912, **10**, 399.
[15] Souques, A. *Ann. de Méd.*, 1926, **19**, 484.
[16] Souques, A., et Bertrand, I. *Ibid.*, 1921, **9**, 305.
[17] Yokomori, K. *Mitt. a. d. Med. Fak. de K. Univ.'s. Tokyo*, 1915, **15**, 1.

A CASE OF RELAPSING INTERSTITIAL HYPERTROPHIC POLYNEURITIS.

BY WILFRED HARRIS, M.D.,

AND

WILFRID D. NEWCOMB, M.B. (CANTAB.).

(*From the Wards and Pathological Department of St. Mary's Hospital, London.*)

SOME of the pathological specimens of the case on which this paper is based were shown three years ago at the Pathological Meeting of the Neurological Section of the Royal Society of Medicine, on May 13, 1926. The opportunity is now taken of publishing the case at the same time as Dr. de Bruyn and Dr. Stern's somewhat similar case, a point of considerable advantage to those interested in studying the subject. As these authors are dealing fully with the literature, we have avoided unnecessary reference to previously published cases.

Clinically, our case may be said to have resembled a relapsing or recurrent polyneuritis, which was the diagnosis made during life, as the man was well nourished, with big limbs, and no observation of the nerve-trunks being enlarged was made during life. Indeed, the great size of the nerve-trunks and of the spinal roots was a surprise to us at the autopsy, the sciatic nerve being so large, 1¼ in. in diameter, that when, six days after death, it was shown at the pathological meeting, a pathologist of experience humorously suggested that we had brought down a bullock's sciatic nerve in place of a human specimen. A photograph of the nerve, cut at the level of the lower border of the gluteus maximus, placed beside a corresponding portion of the sciatic of another man who was rather larger than our patient (fig. 1), illustrates well its great increase in size, even though it had shrunk considerably owing to fixation.

Although the pathological specimens of the nerves in our case resemble both macroscopically and microscopically those originally described by Dejerine and Sottas, and by Dejerine and Thomas thirteen years later, yet clinically our case differs greatly from these. Their cases were familial: a brother and sister who were affected by the disease in childhood had clawed hands and feet, kyphoscoliosis, Argyll-Robertson pupils and suffered with ataxy and severe shooting pains. Gombault and Mallet's case, published in 1889, was diagnosed as one of juvenile tabes, but resembled those of Dejerine and Sottas. Marie's case also had kyphoscoliosis and partial loss of the pupillary reactions to light, but ataxy and shooting pains were absent. These cases might easily be mistaken for juvenile tabes, and have to be distinguished from Friedreich's disease and from the Charcot-Marie-Tooth type of amyotrophy. Roussy's case, published in 1919, more nearly resembles our case in the age of his patient, 44, the absence of deformities, and the normal pupillary reactions.

Our case, however, differs from all those hitherto published with necropsy, in that the chief clinical feature was recurrent attacks of paralysis resembling polyneuritis during six years, with complete recovery between the attacks of paralysis. His last attack of weakness was progressive for twelve months, with muscular wasting and foot-drop, and at the end there occurred attacks of choking, severe dyspnœa, and finally paralysis of the diaphragm, possibly due to the marked degeneration found later in the roots of the vagus and phrenic nerves. In 1897 Sorgo described a case of recurrent polyneuritis in a man of 50, in which a fatal result followed three attacks of paralysis at intervals of a few months, death resulting from involvement of the respiratory nerves and paralysis of the diaphragm. Obstinate constipation was a feature of the case. Extensive disease of the vessels was found in the muscles, peripheral nerves and cord, due chiefly to thickening of the middle coat with narrowing of the lumina. There was no lesion of ganglion cells, but degenerative atrophy of the muscles and nerves. The man had suffered from syphilis many years before, and the vascular changes were attributed to this; Sorgo noted that the symptoms were much more severe than could be accounted for by the microscopical findings, and he assumed widespread dynamic change in the cells of the central nervous system. His case showed no hypertrophy of the nerves and the pathological changes are entirely different to those in our case, the resemblance between them being limited to the recurrent attacks of polyneuritis and a fatal termination with respiratory paralysis.

Nattrass has described a case with three attacks of polyneuritis at intervals of several years, in which the nerve trunks appeared to be palpably enlarged during life; his patient recovered.

D. K., aged 52, a seaman in H.M. Navy, served during the War in a destroyer in the North Sea, being in perfect health. In 1919, when aged 45, he was demobilized, and soon afterwards he had a "nervous breakdown," complaining of weakness of the legs with unsteadiness of gait, especially in the dark, and of tingling and loss of sensation in the tips of his fingers. These symptoms cleared up after several weeks, but he had later had four similar attacks, with complete recovery in the intervals. In March, 1925, similar symptoms again gradually developed, followed by weakness of the feet and hands, and a sensation of pins and needles in the hands and feet. He began to find difficulty in distinguishing coins in his pocket and to drop things, and the muscles of the hands began to waste. His arms became so weak that he could not raise them at the shoulders, and the muscles of the legs wasted and the feet became dropped. There was never any pain, nor any weakness of the sphincters. On applying to the Navy Board for a pension on account of his bad health, he was refused on the ground that he was suffering from progressive muscular atrophy, which was unconnected with his service in the Navy. During February, 1926, he improved slightly in his general strength, though he had several slight attacks of choking. These attacks are of interest in view of the severe attacks of dyspnœa and choking which developed in the last few days of his life. There was no history of any similar disease in other members of his family.

One of us was asked to see him on April 4, 1926, and he was admitted to St. Mary's Hospital on April 14. He then had a steppage gait, with complete bilateral foot-drop, and also considerable weakness of the gastrocnemii and of the flexors of the toes. Flexion and extension of the hips and knees were only slightly weakened. The abdominal and trunk muscles were fair. In his arms the deltoids were weak, so that the arms could not be completely abducted at the shoulder, and flexion of the forearms was also feeble. The supinator longus was thin and small. There was slight wrist and finger drop on both sides, and the intrinsic hand muscles were notably wasted. The grip was poor, and there was well-marked intention tremor of the arms. The movements of his chest were good, the pulse 84, and the heart normal. His pupils reacted normally to light, and slight nystagmoid jerkings of the eyes were observed on lateral movement.

Sensation.—There was slight numbness of the finger tips, and he was apt to let small objects slip from his fingers, but there was no objective loss of tactile sensation or to pin-prick on the hands or arms, trunk, or feet and legs.

Reflexes.—Knee-jerks and Achilles-jerks absent. The plantar reflexes and all abdominal reflexes were also absent. There was no affection of the sphincters. His urine was normal. Electrical testing showed full reaction of degeneration in the leg muscles and in the extensors in the fore-arms.

Treatment by massage and galvanism to the muscles was given on alternate days, and he was given injections of strychnine twice daily, commencing with $\frac{1}{30}$ gr. and gradually increased to $\frac{1}{11}$ gr. after ten days. His condition remained much the same until May 6, when he had three bad attacks of choking. His pulse was irregular, its rate increased to 150 per minute, with respiration 36. He had considerable difficulty in breathing, and the diaphragm appeared to be paralysed. The strychnine injections were stopped, and morphia and atropine were administered, but he never rallied, and he died at 3.20 on the following morning, May 7.

A necropsy was performed ten hours after death, and the following is a summary of the findings:—

A well-nourished man with several pedunculated fibromata on the skin of his back. The muscles of legs and hands were wasted. No thickening of the cutaneous nerves was noted. There was broncho-pneumonia with racemose areas of peribronchial consolidation, surrounded by areas of collapse, in the lower lobes of the œdematous lungs, and parenchymatous degeneration of the liver, kidneys and myocardium.

Nervous system.—The brain, which was preserved unopened in 10 per cent. formol-saline, appeared normal externally. The cranial nerves were not noticeably enlarged.

Spinal cord in its membranes felt thick and elastic as if œdematous, and the meningeal vessels were injected. On opening the dura the thickening was seen to be due entirely to a great increase in size of the nerve-roots, especially those forming the cauda equina, which had a curious purplish colour. The posterior root ganglia were less conspicuous than usual. The left sciatic nerve was much enlarged, measuring 3·7 by 1·5 cm. at the level of the lower border of gluteus maximus muscle. It had a swollen, soft glistening gelatinous appearance. On section each individual fasciculus appeared changed to a clear, partly translucent cord which, although feeling soft, was tough to cut. The fibrous tissue in the nerve-sheath and that between the fasciculi appeared normal. A high bifurcation, shortly below the gluteus maximus, was present. The left median nerve showed similar changes.

The brain, spinal cord, sciatic and median nerves were preserved in 10 per cent. formol-saline. Frozen sections were stained with Sudan-III and hæmatoxylin, and by the Weigert-Pal and Bielschowsky's silver methods. Paraffin sections were stained with Ehrlich's hæmatoxylin and eosin, Weigert's iron hæmatoxylin and van Gieson's stain, Weigert's elastin stain and neutral red, Mayer's mucicarmine and toluidin blue for Nissl bodies. Some material was transferred to Müller's fluid, and after three months was embedded in paraffin and the sections prepared by the Weigert-Pal and van Gieson stains. Other blocks were fixed in Bouin's fluid and the sections stained by Mallory's acid fuchsin, aniline blue and orange G method.

Microscopical appearance. Sciatic nerve.—The epineural fibrous sheath appears normal, but the interfascicular fibrous tissue contains thin collagen fibres separated more widely than usual by œdema.

The perifascicular sheaths are thrown into irregular folds owing to the shrinkage of their contents during the fixation and preparation of the sections. This shrinkage is a remarkable feature of the fasciculi. It causes diminution in size of the macroscopic specimen seen in the photograph of the Kaiserling preparation (fig. 1), where the nerve has shrunk from 3·7 to 2·2 cm. in width. It is most marked in paraffin material, but can also be seen in frozen sections. The folds are extremely irregular, giving the cross-sections of the bundles an appearance resembling a map of a rocky archipelago in which the islands have numerous capes and bays. A single fasciculus is seen in fig. 2. On the inner surface of the perineurium, and running from it between the nerve-fibres into the centre of the fasciculi, is a peculiar acellular clear material (*a* and *b*, fig. 2).

The amount of this substance varies in different fasciculi and in different parts of the same fasciculus. Often it is thick and dense at one side (*b*) and thinned out into strands at the other (*a*). There is always more at the periphery, where it may reach 100 μ in thickness, than between the nerve-fibres. This substance stains faintly blue with hæmatoxylin, pink with neutral red, yellow with Van Gieson's stain, bright pink with eosin, and orange with Mallory's stain. A few lamellæ in the more condensed portions can be stained with the Weigert-Pal method or with neutral red; hence it may be called amphophile, but its nature is quite unknown. The laminated appearance is probably an artefact due to fixation and dehydration. The substance is evidently the same as the clear interstitial substance described by Marie and Bertrand in their case [1].

Mixed with the amphophile substance there is a little mucinoid matter at the periphery of the nerve, and much more between the nerve-fibres. This stains with Mayer's mucicarmine in threads, as shown in fig. 4. There is also present a considerable amount of fluid coagulated by the fixative which scarcely stains. Thus the endoneurium is given an appearance similar to the subcutaneous tissues in myxœdema.

The most noticeable change in the nerve-fibres is the formation of several more or less concentric layers of fibres giving the remarkable "onion bulb" appearance described by Dejerine and most other authors; it can be seen in fig. 3. This seems to be due mainly to a proliferation of the sheath of Schwann and its cells. The cellular proliferation is very great. As in the normal nerve, there is only one

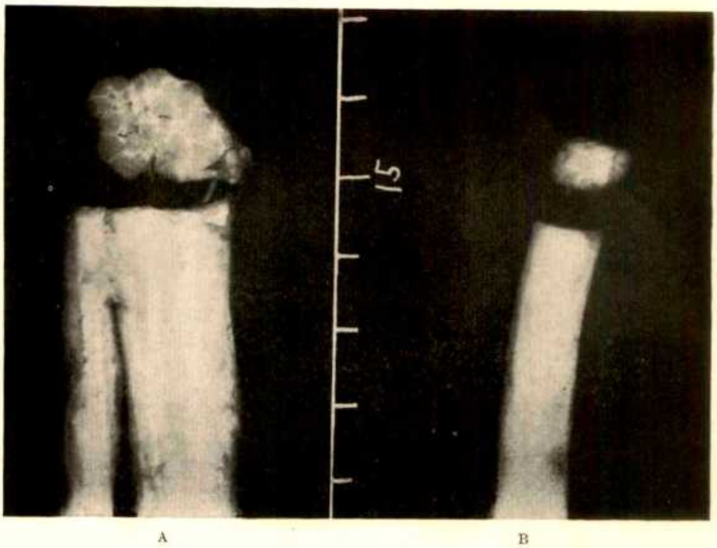


FIG. 1.—Photograph of the affected great sciatic nerve A, together with one B, from a normal fat man. The cross-section shown in each case is 1 cm. below the lower border of the gluteus maximus muscle. Scale in centimetres.

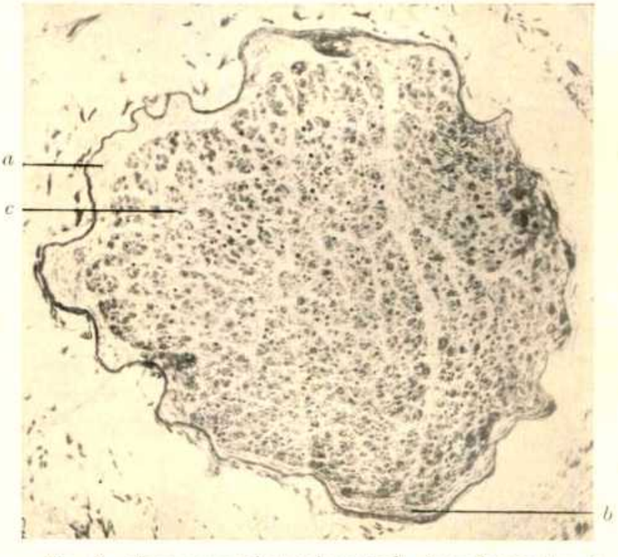


FIG. 2.—Low-power photomicrograph of one fasciculus of the sciatic nerve. It shows the irregular outline, peculiar interstitial substance, *a*, and the laminated appearance in the more condensed part, *b*. The few myelin sheaths remaining appear as dark dots, *c*. Weigert-Pal and van Gieson.

To illustrate Dr. Wilfred Harris's and Dr. Wilfrid D. Newcomb's article.

nucleated cell to each internode, the chance of seeing a nucleus in any cross-section is small, but here the average number of nuclei to any cross-section of a fibre is three, and frequently as many as six nuclei may be found around a single fibre.

It is difficult to be certain if all these laminæ are formed from the sheath of Schwann, or if the fibrous sheath of Henle also takes part. The outer layers are formed of collagen fibres which stain normally and have thin, elongated darkly-stained nuclei. The inner layers stain a brighter pink with eosin and have a yellower tinge with van Gieson's stain. Many of the nuclei are rounder, stain less deeply, and have a fine reticular pattern, resembling more closely the normal cells of Schwann. There seems little doubt that these central cells and fibres are formed from the sheath of Schwann, but whether the outer ones are of the same origin and older, or whether they are formed from the fibrous sheath of Henle, is not certain.

The myelin sheaths are usually destroyed. In several fasciculi none are present, but usually a few can be seen (fig. 2). The number varies considerably in different fasciculi. A few sheaths are practically normal, but most are in various stages of degeneration; some appear as thin or dotted rings, poorly stained by the Weigert-Pal method, others as thick, swollen club-shaped masses.

The axis-cylinders are difficult to demonstrate, and the preparations stained by Bielschowsky's and Malory's methods are not easy to interpret. In nearly all the fibres there is something stained by the silver which might be an axis-cylinder. Many of the larger "onion bulbs" contain several small fibrils, and others a large stained area. There are also a number of stained fibrils entirely outside the sheaths. These appearances have been interpreted as axons in various stages of degeneration and regeneration. As there is no sign of axonal reaction in the anterior horn-cells (fig. 8), it is unlikely that the axis cylinders of the motor nerves have been destroyed.

To summarize the main features of the sciatic nerve: Axis-cylinders are usually present, but the myelin is mostly destroyed; the neurolemmal sheaths have proliferated and formed "onion bulbs"; mucinoid and œdematous material is present between the nerve-fibres, and the fascicular sheaths are irregular, and contain the peculiar amphophile substance.

The median nerve shows a similar appearance, but the changes are less advanced. There is little of the peculiar amphophile interstitial substance, and when it is present it is confined to the periphery of the fasciculus just beneath the perineurium. The myxœdematous condition of the endoneurium is well marked, and contains as much mucinoid material as the sciatic nerve. The "onion bulb" arrangement of the proliferated sheath of Schwann is present, but is not as prominent. A conspicuous feature is the variation in the amount of demyelinization in the different fasciculi; in some all the myelin has disappeared, while others contain nearly as much as normal and the sheaths themselves are thicker.

The posterior root ganglia were relatively inconspicuous. This is probably due to the increase in size of the nerves overshadowing the ganglia, which are not enlarged. There is no obvious lesion in the ganglia (fig. 9). Some cells are crenated, and in some the nucleus is excentric, but no stress can be laid on such changes in fixed dehydrated sections. Marie and Bertrand, 1918, and Souques and Bertrand [2], 1921, both describe these changes as significant, but they would seem more likely to be artefacts. The Nissl bodies appear normal. The nuclei in the pericellular sheath seem prominent, but they are just as numerous in a normal control. Ganglia from the lumbar, dorsal, and cervical regions were examined, and all were similar.

The nerve-roots examined all showed some degree of degenerative changes in the myelin sheaths and varying amounts of proliferation of the sheath of Schwann. There is considerable variation in different fasciculi of the nerves, and also from root to root, but on the whole the changes become more advanced from above downwards. Even in the cauda equina they are not nearly so marked as in the sciatic nerve. As a general rule the change is more pronounced in posterior than anterior roots, although this is not quite constant. None of the interstitial clear substance has been found in the roots, and only very small amounts of the mucinoid material. The fibrous proliferation around the fibres is present, especially in the lower roots, but the "onion bulbs" are smaller and thinner than those in the peripheral nerves. The changes in the myelin sheaths are very variable, but always there is less degeneration than in the corresponding peripheral nerves. Towards the upper end of the cord the myelin is frequently in irregular rod or club-shaped masses, with a small surrounding fibrous sheath. A similar change is present in the lower cranial nerves, being particularly well shown in the root of the vagus, where the thickness of the fragments of myelin is very striking. Several vagal fibres are completely demyelinated, as seen in fig. 7.

Unfortunately, neither the vagus nor the phrenic nerves were preserved, but as the changes in their roots are well marked, it may be assumed that both suffered similar changes to the median.

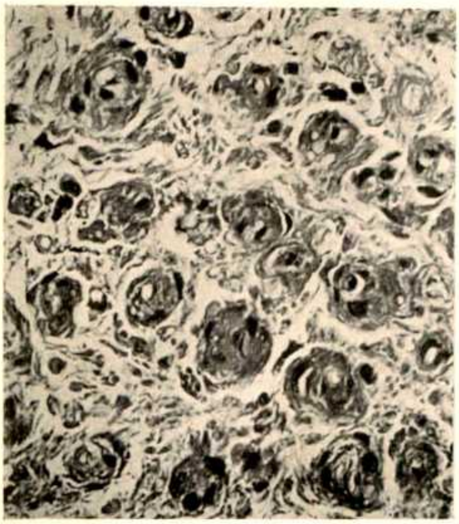


FIG. 3.—High-power view of a cross-section of the sciatic nerve, showing "onion bulbs" with interstitial substance between. Iron hæmatoxylin and van Gieson.

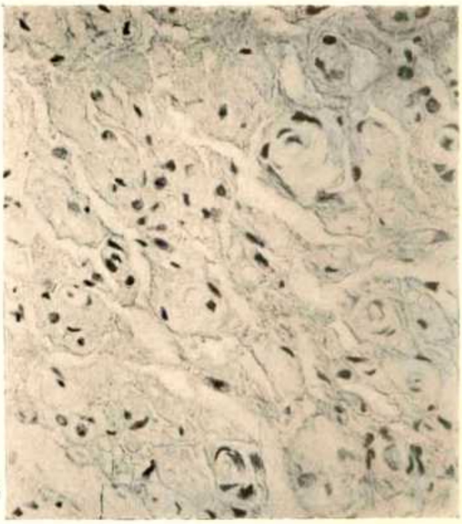


FIG. 4.—The same section stained with Mayer's mucicarmine. The strands of mucinoid material appear light grey.

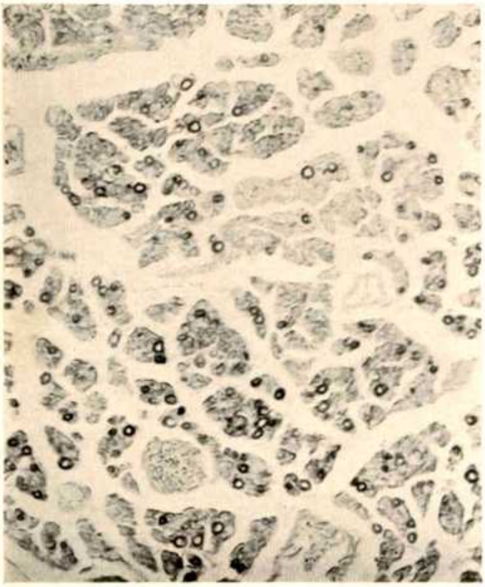


FIG. 5.—Cross-section of the posterior root of the fifth lumbar nerve, showing few medullary sheaths and much proliferation of the sheaths of Schwann. Weigert-Pal and van Gieson.

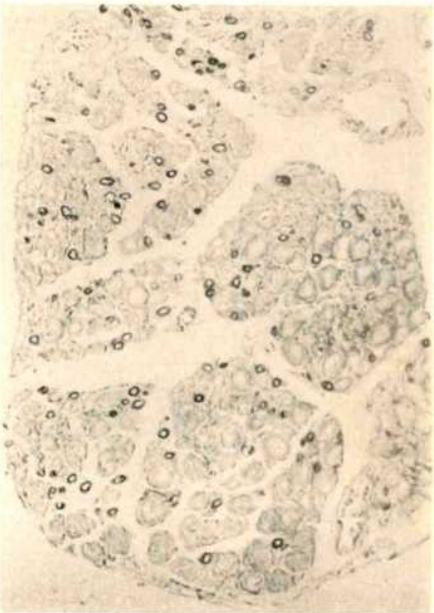


FIG. 6.—Cross-section of the anterior root of the first dorsal nerve, showing small "onion bulbs" and few medullary sheaths. Weigert-Pal and van Gieson.

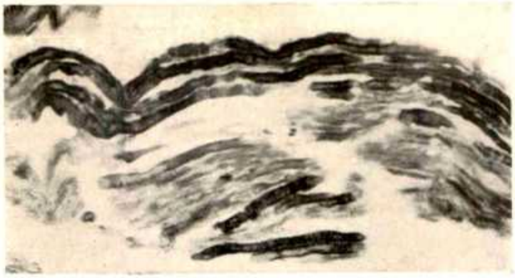


FIG. 7.—Longitudinal section of the root of the vagus showing the black masses of degenerating myelin and grey areas of collagen fibres. Weigert-Pal and van Gieson.

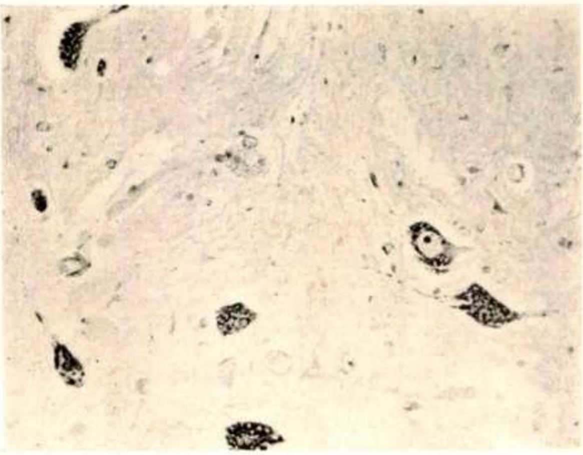


FIG. 8.—Anterior horn-cells of the second dorsal segment. (Normal.) Nissl method.

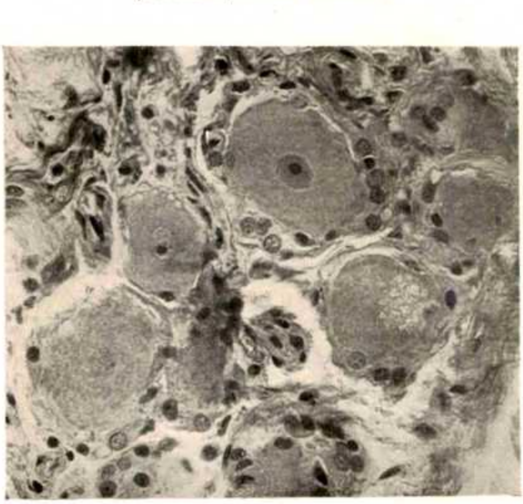


FIG. 9.—Mid-dorsal posterior root ganglion. (Normal.) Iron hæmatoxylin and van Gieson.

The highest root examined was that of the third cranial nerve; it shows the earliest lesions, viz., œdema separating the nerve-fibres and commencing fibrosis around them. It is noteworthy that here, where the change is just starting, there are only a few scattered lymphocytes present, no more than in a normal nerve. In fact, it may be stated that nowhere throughout the nerves examined in this case was there any sign of leucocytic infiltration, which agrees with most of the previous cases recorded, but Souques and Bertrand, 1921, lay considerable stress on the presence in their case of lymphocytes, plasma cells, and other wandering cells.

Where this case differs from all other necropsy records is in the spinal cord, which for the most part is quite normal. The dorsal and cervical regions show no signs of degeneration. In the lower lumbar region there is a vague thinning of the posterior columns in a Weigert-Pal preparation, as viewed with the naked eye. Microscopically the myelin sheaths in this area are in the form of dotted rings instead of complete annulets, but none have completely disappeared. As there is no sign of degeneration in Goll's column in the upper sections, it does not look as if any of the long ascending fibres in this part can have been destroyed.

The nerve-cells in both anterior (fig. 8) and posterior horns, as seen in Nissl and hæmatoxylin preparations, appear normal. The cells of Clarke's column also show no abnormality.

In sections at the level of the olive, the vagal fibres passing between the nuclei and the issuing roots appear normal, while immediately outside the medulla they commence to degenerate. This abrupt change coincides with the beginning of the sheath of Schwann and suggests that the essential lesion is its proliferation.

In this case there is no evidence of true inflammation. It would seem that the change is more in the nature of a hyperplasia similar to that seen in the breast in the so-called "chronic mastitis."

Recurrent attacks of polyneuritis without obvious cause, such as lead or alcohol, have been published by many authors, by Grocco in 1885, Ross and Bury in the case of two sisters, by Sorgo, by H. M. Thomas in 1898, in the case of a man, aged 28, who had five attacks of paralysis within six years, and by others (see *Brain*, vol. xlv, p. 427). In none of these, however, has hypertrophy of the nerves been discovered, except in the case described by Nattrass in a boy of 18, with double foot-drop, loss of the deep reflexes, and other signs of generalized multiple neuritis, in whom the nerve-trunks were palpable and appeared to be enlarged. This patient had had two previous attacks of paralysis at the ages of 4 and 17. As this case did not end fatally, it is not possible to assume that the nerve-changes were comparable with those in our case.

It seems that the Dejerine and Sottas type of familial hypertrophic interstitial neuritis should be distinguished as a separate group from recurrent polyneuritis, to which our case appears to belong, though the interstitial hypertrophic neuritis found in the nerve-trunks and spinal nerve-roots in our case forms a remarkable link between the two groups, and it is conceivable that a similar underlying cause may be responsible for all of them, as an autotoxæmia from an enterotoxin, such as is the probable cause in hæmatoporphyrinuric polyneuritis.

In conclusion, we should like to express our thanks to Dr. J. G. Greenfield for his help in taking the photomicrographs.

REFERENCES.

[1] MARIE, P., et BERTRAND, I. *Annales de Med.*, 1918, **5**, 209.
[2] SOUQUES, A., et BERTRAND, I. *Ibid.*, 1921, **9**, 305.

NOTICES OF RECENT PUBLICATIONS.

The Cytoarchitectonics of the Human Cerebral Cortex. By CONSTANTIN VON ECONOMO. English translation by S. Parker. Pp. 186, with 61 Illustrations. London: Humphrey Milford. 1929. Price 21s. net.

Notices of the German and French editions of this book have already appeared in this Journal and we now welcome an English translation. The design of the original has been hardly altered and the numerous whole-page illustrations are reproduced on almost the same page and in the same relation to the text as they occupy in the original book. We could wish, however, that the translator had not followed the original so exactly in some respects, as a too literal translation of the German has made the text either unintelligible or misleading in many places. For example, he speaks of a "clear nucleolus" and a "fat vacuole" in nerve cells. In fact it is often necessary to refer to the German or the French edition to arrive at the author's meaning. We could wish too that, instead of the long chapter headings of the original, the translator had adopted the useful paragraph headings of the French edition, which greatly excels the English edition both in the translation and in the reproduction of the plates. The latter fault is presumably due to the quality of the paper used, and may be improved in later printings, but it greatly detracts from the value of the book. In spite of these shortcomings, however, the book will be of value to many who prefer to have anatomical textbooks in their own language.

Tumours arising from the Blood-vessels of the Brain. Angiomatous Tumours and Hæmangioblastomas. By HARVEY CUSHING and PERCIVAL BAILEY. Springfield and Baltimore: C. C. Thomas. Pp. 219 with 159 Illustrations. 1928. Price 34s.

This book deals with rare forms of tumour, of which the authors have only met with twenty-nine examples in a series of 1,522 intracranial tumours. Of these twenty-nine, six were venous angeiomas, nine arterial (arterio-venous) angeiomas, one a telangiectasis and thirteen hæmangeioblastomas (plexiform angeioma). It is remarkable that all the venous angeiomas were supratentorial, and all the hæmangeioblastomas subtentorial. This must be considered purely fortuitous as regards the venous angeiomas, as cerebellar or pontine examples are not uncommon, but it agrees with the experience of most other observers, especially Lindau, who could find no example in the literature of a supratentorial hæmangeioma.

The first half of the book deals with the arterial and venous angeiomas and the case of telangiectasis. None of these cases has been very favourable for operation. In one case of arterial angeioma and one of venous angeioma the tumour was successfully removed and several other cases appeared to be benefited by simple decompression, or by ligature of arteries in the neck. X-ray treatment was used in most cases but proved of doubtful value. On the whole the authors recommend simple decompression for these classes of tumour.

The second half deals with the cerebellar hæmangeioblastomas. Of these, seven were in the walls of cysts, and the other six were rather large solid tumours. In this class of growth the operative mortality was high, as four patients died within forty-eight hours of operation. But in four cases complete, and in three cases partial, removal of the growth was successfully performed.

In discussing diagnostic and therapeutic possibilities in relation to the venous, arterial and telangiectatic forms, the authors comment on the difficulty of a pathological diagnosis and the impossibility in the majority of cases of dealing with the disease in a radical manner. In the cerebellar hæmangeioblastomas also it was impossible at the time when the patients came under observation to form an opinion as to the nature of the growth, although a later examination of one patient revealed a retinal angeioma and family history of similar cerebellar disease.

In dealing with so rare a type of tumour the authors have taken the only possible course in writing a monograph rather than a textbook. Full reports are given of a large proportion of the cases, and the literature dealing with the subject is fairly exhaustively surveyed. Altogether it is a useful and informative book; perhaps most useful in being largely a record of unexpected difficulties met at operation, and of wise retreat when advance appeared too hazardous. As minor criticisms we note that the common picro-fuchsin counterstain is always spelt " van Giesen," and that the authors persist in the use of the name " meningioma " in spite of a general agreement that the name of a tumour should be taken from the tissue, and not from the anatomical structure, from which it arises.

Epilepsy, from the Standpoint of Physiology and Treatment. By W. C. LENNOX and STANLEY COBB. Pp. 197. London: Baillière, Tindall and Cox. 1928. Price 16s.

This monograph is a critical survey of our present knowledge of the nature of the pathogenic factors concerned in the occurrence of epileptic seizures, whether associated or not with any demonstrable structural disturbance in the central nervous system. The authors' own investigations, valuable though they be, take a subsidiary place to the review of observations and theories, old and recent, which have been put forward by others. The only criticism of the book that can be suggested is, in fact, its comprehensiveness; even the views of abdominal surgeons and of non-professional bacteriologists are included, for the aim of the authors is to assimilate all available evidence.

The interesting critical review of the neurological mechanisms of convulsions includes the irritation, release, " short-circuit " and explosive theories, one of which alone is regarded as sufficient, though it is suggested that the explosive theory, according to which the seizures result from some sudden metabolic change in the nervous system, may finally explain the epilepsies. Functional abnormalities in the nervous tissues of a physico-chemical nature, as disturbance in oxygen consumption, ionic equilibrium, hydrogen-ion concentration and in the permeability of the cell membranes, are also fully considered, but the present state of our knowledge does not permit even tentative conclusions as to the part these play. A search for the exciting causes of seizures in abnormalities in other systems, in metabolism and in the acid-base relationships, occupies the greater part of the book; the profusion of theory and the poverty of definite facts, so prominent in the literature of epilepsy, is strikingly illustrated in these pages, but the critical study of these subjects which the authors give us will be extremely useful to all interested in the subject. They personally find the essential elements in the precipitation of the seizures to be " oxygen lack," alkalosis and a disturbance of the water-balance of the tissues. Further investigation will determine the importance of these and other factors, but it is to be hoped that the innate or acquired disturbances in the brain that the authors admit to exist in all cases in which the epilepsies occur, will not be lost sight of. Many changes in the fluids of the body can excite convulsions in both the normal and predisposed, but there is as yet no compelling evidence that in epilepsy the immediate as well as the predisposing cause of the seizure does not lie in the brain.

Die Vorder- und Mittelhirnganglien des Menschen als plastische Gebilde. Von B. SCHLESINGER. S. 55. Berlin: J. Springer. 1928. Price M. 6.60.

The anatomy of the internal structures of the brain is usually studied in sections through it, and their topographical relations are learned by a mental piecing together of sections in different planes. Reconstructed models in wax and other substances may be, however, employed for teaching purposes, but it is obviously preferable to demonstrate these structures in preparations of the brain itself. The author describes a series of dissections by which this can be done, describes and figures the preparations, and supplies a series of stereoscopic photographs of them which should be valuable in the teaching of students and in a revision of the anatomy of this complicated region.

Anatomy and the Problem of Behaviour. By G. E. COGHILL. Pp. 113. Cambridge: The University Press. 1929. Price 7s. 6d.

This book is based on a correlated series of studies on the development of behaviour and on the growth of the nervous system in an amphibian, Amblystoma. The simplest reactions of the embryo from the egg stage are first described, and later the swimming mechanism, the movements and local reflexes of the limbs. Terrestrial locomotion and the feeding reactions are also analysed in relation to the structure of the maturing nervous system. The embryo is, however, perfectly integrated before it possesses a nervous system, and the second chapter deals with the dynamic antecedents of the neural mechanisms, as the appearance of polarity and of the so-called metabolic, axial and other "gradients," and their influence on the developing nervous system, the paths of which are determined largely by the preneural activity of the tissues. In the final chapter on the growth of the nerve cell and the interpretation of behaviour, emphasis is laid on the view that behaviour does not depend merely on a combination of reflexes, but that there is an organic unity from the beginning, in fact the central mechanism of a reflex is developed long before the reflex itself appears.

How to Stain the Nervous System. By J. ANDERSON. Pp. 139. Edinburgh: E. and S. Livingstone. 1929. Price 5s.

The only textbooks on the histological examination of the nervous system in English are either too detailed for the novice, or do not include some of the most recent methods of staining. This small book by the chief Laboratory Assistant at the National Hospital is consequently welcome and will be of the greatest value to the laboratory technician as well as to the student of neuropathology. All the methods described in it have been used by the author in his routine work, some of them or modifications of other methods have, in fact, originated from him, and they can therefore be accepted as the most suitable and reliable now available. They are all described clearly and concisely, and a short résumé follows the detailed description of each procedure. In addition to staining he deals with the best means of preparing the tissue, of cutting sections, of obtaining serially stained sections, and other procedures which have been evolved from a long practical experience.

Handbuch der Geisteskrankheiten. Herausgegeben von OSWALD BUMKE. Erster Band: Allgemeiner Teil, I. S. 732, mit 44 Abbildungen. Price RM. 68.80. Dritter Band: Allgemeiner Teil, III. S. 333, mit 77 Abbildungen. Berlin: Springer. 1928. Price RM. 34.40.

This System of Psychiatry will probably take the place which Aschaffenburg's notable "Handbuch" has occupied for the last two decades. Unlike the latter, it has no Swiss or Austrian contributors; it is wholly German, but it is none the less complete or distinguished for that.

The general tone of the work is indicated by the Editor's introductory article on the aims, ways and limits of psychiatric research. Bumke considers psychiatry as essentially one of the natural sciences, calling for an exact essentially objective determination of facts and for strict logical reasoning: it must not set about translating into the language of neurology or cerebral pathology psychological facts whose physiological correlates are unknown, nor must it deal in the "metaphysical-romantic." The "neurologizers" he handles rather kindly, but at the psycho-analysts he girds with caustic vigour. His survey is wide and severely critical.

The history of psychiatry is dealt with by Birnbaum; he gives little attention to other than German schools, but this proves to be no impediment to the lucid setting forth of the main lines along which psychiatric thought and research have travelled.

The next section, on Inheritance, by J. L. Entres, is a monograph of great thoroughness; it professes to be no more than a compilation, but in this confused field a faithful inquiry into all that has been written and an ordered presentation are of great value.

A brief survey of acquired somatic causes by Korbsch is followed by articles on external psychic causes and on structural analysis by Kehrer, with a useful appendix on the anamnesis. These end the section on etiology. The rest of the volume is given up to general symptomatology.

The pathology of perception is dealt with exhaustively in two papers by Stein and Mayer-Gross, whose original work in this connection has been so distinguished. Disorders of memory are discussed by Kurt Schneider, disorders of thought by Jahreiss, who also deals with disorders of consciousness. Kretschmer's comprehensive yet brief consideration of disturbances of affective life, and Stertz's article on disorders of intelligence conclude the volume.

The other volume published deals with the bodily changes that may be associated with mental disorders. It is fittingly introduced with a balanced account of what is known as to the relation between physique or habitus and psychic predisposition—a field in which much work is being done in Germany and America, and in which extravagant claims are sometimes made. Neurological changes in mental disorder are described by Rosenfeld almost too thoroughly; one has at times the impression that one is reading a somewhat long-winded textbook of neurology, but at any rate nothing is omitted. Küppers writes on the pulse, blood-pressure, vasomotor changes and distribution of blood; Wuth resumes what had been learnt about body-weight, the endocrine system and metabolism in this connection by 1926, when the article was written; and with Kafka's authoritative paper on humoral pathology, a valuable addendum to his monograph in "Aschaffenburg," the volume ends.

One cannot summarize contributions of such scope as these, nor profitably discuss them, in a brief review. The work as a whole is admirable, well-proportioned and trustworthy. If one may judge by the two important volumes so far published, Prof. Bumke's hope that it shall give as complete an account as possible of the present state of our knowledge, and at the same time help towards attaining a new and higher standpoint, seems likely of fulfilment.

Die Gegenwärtigen Strömungen in der Psychiatrie. Fünf Vorträge von OSWALD BUMKE. S. 111. Berlin: Julius Springer. 1928.

The five papers here collected were written for various gatherings between 1924 and 1927, and make Professor Bumke's conservative position clear. There is of course some repetition, but on the whole one finds a discerning survey of the various tendencies in psychiatry now and during the last few years.

The treatment is rigorously critical, especially in the numerous passages devoted to psycho-analysis; onslaughts with horse and foot follow tempered, even niggardly, appreciation.

The little book is attractively written and is well worth reading as the expression of wide knowledge and a clearly-defined point of view.

Subordination, Autorität Psychotherapie. Von ERWIN STRANSKY. S. 69. Wien: J. Springer. 1928.

The relation of patient to doctor has been studied closely by Freud and his followers, and in the word "transference" much fundamental psycho-analytical doctrine is implicit. Professor Stransky, writing as a "clinical empiricist," joins issue with the Freudians. It is essentially, he maintains, the relation of subordination to authority, a "transsexual" matter, that is concerned. He reviews education, religion, government, social life and authority in general in this light, and sets forth a method of psychotherapy for which he claims good results. He remarks justly that time-consuming methods such as analysis cannot be applied to large numbers of patients, and offers a substitute that is not exclusive of other therapeutic measures. His method, however, does not differ in practice from that of many psychiatrists untroubled by theories which assert a dominance over the patient and make use of the situation of dependence thus brought about, without being able to manage or dispose of it other than crudely. This crux the writer does not elucidate.

The critical and casuistical passages are interesting but not convincing.

Two Essays on Analytical Psychology. By C. G. JUNG. Translation by H. G. and C. F. Baynes. Pp. 280. London: Baillière, Tindall and Cox. 1928. Price 10s. 6d.

These essays, much altered from the first edition which appeared in 1916, are written for the "cultured layman," and it is to him that they may be expected to appeal. Speculation of this sort is fascinating, no doubt, and stimulating; but it cannot sufficiently account for its evidences even when it professes to be based on clinical experience. This book is, however, excellent as a literary work, lucidly presenting difficult, if not mystical, conceptions and provoking thought; one can understand why so many of Jung's non-medical adherents are evangelists of a cult.

The translation is faithful and clear, but the translator's preface contains an unfortunate mixture of adulation and misstatement. Jung is a distinguished psychiatrist; he is not Sakyamuni.

Practical Clinical Psychiatry. By EDWARD A. STRECKER and FRANKLIN G. EBAUGH. Second Edition. Pp. 458. London: H. K. Lewis and Co. 1928. Price 18s.

This is a useful compendium of psychiatry as currently taught in America. It is presented chiefly in the form of case-histories and discussions, with brief formal accounts of diagnosis, treatment, &c. It is clearly not intended for psychiatrists so much as for medical students and general practitioners. It is usually sound and reflects in the main Adolf Meyer's teaching. Occasional statements, such as those regarding the superiority of luminal to bromide in the treatment of epilepsy, or the assertion that in morphine addiction "the hyoscine treatment has proven of value in replacing the narcotic" are open to considerable objection. The frequent use of the word "præcox" as a noun and as an adjective synonymous with schizophrenic is irritating.

Die Psychosen der Schwachsinnigen. Von RUDOLF NEUSTADT. S. 188. Berlin: Karger. 1928. Price RM. 15.60.

The relative poverty of content in the psychoses of mentally defective persons has probably been the main reason why so little investigation into them has been made. Kraepelin's views on "Pfropfhebephrenie" stimulated interest in the relation of dementia præcox to congenital mental defect, but it is only recently that much attention has been paid to the whole subject. It is obviously one of considerable importance, not only on psychiatric grounds but also in its social, especially eugenic, implications.

The author states the evidence which he has required before deciding that feeble-mindedness, a condition of "stationary intellectual defect," was present; he has examined 209 such cases in which psychosis occurred, and by psychosis he understands "morbid, i.e., foreign and novel, psychic phenomena through which the individual line of psychic development is interrupted, temporarily or permanently." The histories of thirty-three of the patients are given in some detail: in a few of these the diagnosis of mental defect is not beyond cavil, but unless he has restricted his investigations to incontestable idiots such doubts could not well be avoided.

He deprecates the assumption that schizophrenia often develops in mentally defective persons; he holds that it is very rare and that in many supposed cases schizophrenic symptoms have appeared at so early an age that they have been regarded as evidence of mental defect, or that the latter diagnosis has been made on the ground of social maladaptation rather than of proven intellectual defect. He is inclined with his teacher Sioli to group together all the conditions he describes and to regard them as a special form of exogenous psychosis, conditioned by the exogenous factor, mental defect—in short mental defect indicates "not a disposition to any possible psychosis but only a specific disposition to the episodic psychoses here described."

Die psychopathischen Persönlichkeiten. Von KURT SCHNEIDER. S. 86. Leipzig und Wien: Franz Deuticke. 1928.

The first edition of this valuable work appeared in 1923; since then investigations into personality and character have been so numerous and fecund that much has been added to the first section of the book, dealing with general considerations, and much made more precise.

All psychopathic personalities are regarded by the author as abnormal in the sense of being different from the average, rather than different from a teleologically conceived ideal norm. They either suffer from their abnormality, or cause suffering to society through their abnormality. The implications and difficulties of this conception are discussed fully, the delimitation of psychopathic personalities from psychoses briefly sketched. Development, somatic basis (chiefly in connection with the doctrines of Kretschmer and of the brothers Jaensch) and the grounds for systematic subdivision are dealt with lucidly and carefully. The second part of the book is descriptive, with appropriate notes on the social significance, relation to psychoses and treatment of the varieties of psychopathic personality.

The book is admirably concise and restrained; it gives a complete picture, according to current German psychiatry, of the people who fall short in their human relationships.

Die Störungen des Bewusstseins. Klinish-diagnostische Studien von Prof. M. ROSENFELD. S. 247. Leipzig: Georg Thieme. 1929. Price M. 18.

This is a careful account of the disorders of conciousness. The author insists that all psychopathological phenomena must be observed and evaluated in immediate reference to the whole psychic state, i.e., the state of consciousness; much is therefore subsumed under this heading.

In a chapter on the manisfestations of unconscious psychic happenings it is pointed out that psycho-analysis can investigate the content of delusions and hallucinations and the relationship of these to experiences that have become unconscious, but that for a diagnostic judgment it is the manner in which they come and go and the patient's reaction to them that are decisive. "It is not what the patient says or hallucinates or dreads that matters, but how he experiences these happenings."

In an interesting discussion of the connection between cerebral processes and disorders of consciousness, the author goes into the problem of sleep and the mode of action of narcotics; he mentions, and is evidently rather taken with, Semon's assumption of an irritable substance in the cerebral cortex.

In the general symptomatology, besides the psychic manifestations, neurological and general somatic concomitants are dealt with systematically. Then follows the description of the pictures seen in special disorders. The author incidentally defines his attitude towards such matters as the distinction between "psychogenic" and "hysterical" disturbances, and the diagnostic criteria of manic-depressive insanity and the schizophrenic group.

There are numerous references and a good index.

Psychologie. Von HARALD K. SCHJELDERUP. S. 330, mit 20 Figuren im Text. Berlin: Walter de Gruyter and Co. 1928.

This is a translation into German of a recent work by the Professor of Psychology at Oslo University. He has set himself the task of combining the findings of the various schools and giving an integrating survey in which "the more classical experimental-psychology shall be fused with the results of behaviourist studies, as well as with those of psycho-analysis, into an organic unity." Watson and Freud, therefore, bestride the book; the harmony is not always satisfying. The author does not neglect discussion of other recent work, though one looks in vain for an appreciation of Pawlow's researches or of Spearman's.

The book is divided into sections, on the original equipment, the mnemic functions, and the personality and its conflicts, with a final summary of the practical applications of psychology.

The author is evidently widely read, but appreciative rather than discriminating; he is constantly mindful of the human being he is writing about, and so his book remains interesting and relevant: he often adduces psychopathological problems and illustrations. The exposition throughout is lucid and consecutive.

A Study of Intercranial Surgery. By HUGH CAIRNS. Pp. 83, with 30 plates. London: H.M. Stationery Office. 1929. Price 3s.

This brochure, published by the Medical Research Council, contains the impressions of a student gained during a year spent with Dr. Harvey Cushing. His aim is to recount the methods employed in this clinic in the diagnosis and treatment of intercranial tumours; he contributes nothing new to the subject, nor attempts a critical review of the many problems that it presents. He records the case histories of 32 patients, some of which had been previously published, in order to illustrate the difficulties of diagnosis and the surgical methods employed in their treatment. Thirty plates are appended containing a large number of figures, some of which have been printed before, but many are only reproductions of temperature and other charts after operations, or photographs of healed wounds.

The Child of Circumstance. By ALBERT WILSON. Pp. 420. London: John Bale, Sons & Danielsson, Ltd. 1928. Price 15s. net.

The increase of interest in criminology is evidenced by the numerous books that have been lately devoted to it, chiefly from the psychological side. The late Dr. Wilson devoted much time to its study, though from the humanitarian rather than the scientific side, and has published several books and articles relating to it. This volume scarcely substantiates his claim to deal with the criminal from a scientific point of view, for it shows little insight into many of the problems crime and the criminal present, but it is readable and recounts interesting observations in a clear and intelligent form. It is unfortunately diffuse, including chapters on Lord Lister, Quakerism and other matters that are really not relevant, while there is too much theorizing on pathological and biological problems involved, and a striking neglect of recent investigations.

Mikroskopische Anatomie des Vegetatives Nervensystems. Von P. STÖHR, JR. S. 251 mit 243 Abbildungen. Berlin: J. S. Springer. 1928. Price 36 M.

The vegetative nervous system will certainly in the future occupy a more important place in clinical medicine than that at present allotted to it, and a more exact knowledge of its anatomy must precede any attempt to establish a rational pathology of it. We have been for long acquainted with the topography and distribution of its main tracts, and from the work of Langley and others, with the chief principles of its construction, but our knowledge of the peripheral distribution of the sympathetic and parasympathetic fibres to various organs of the body has been patchy and dependent on numerous separate articles widely scattered throughout the literature. In this beautiful monograph Stöhr has furnished a comprehensive account of all the elements of the vegetative system, and illustrated his descriptions by numerous figures, both original and borrowed, some of them in colour. The excellent reproduction of these illustrations is one of the features of the book that deserves the highest praise.

The nerve-supply to the blood- and lymph-vessels, to the endocrine glands and smooth muscles, as well as to the various visceral organs, is described in detail in separate sections. Preceding work is liberally but critically reviewed, and in many instances the physiological significance of the anatomical arrangements is discussed. The volume can be strongly recommended as a classical textbook and as a useful work of reference.

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-91, Great Titchfield Street, London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I to XXIII inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.

CALCUTTA UNIVERSITY LIBRARY
Acc. No.........
Book No.........

JULY, 1929.

BRAIN.

PART 2, VOL. 52.

A CLINICAL STUDY OF TWENTY-ONE CASES OF TUMOUR OF THE HYPOPHYSEAL STALK.

BY J. W. BECKMANN, M.D.,

AND

*L. S. KUBIE, M.D.

* *Travelling Fellow, Medical Fellowship Board, National Research Council, Washington, D.C.*
(*From the National Hospital, Queen Square, London.*)

INTRODUCTION.

INTEREST in the tumours which form from cell-rests of the neural and stomodæal contributions to the hypophysis began with the studies of Erdheim [20] in 1904. By 1920 Duffy [18] was able to collect sixty reports of similar cases; and since then there have been many more descriptions, most of which will be referred to in the succeeding pages.

In the same study Duffy, and later Critchley and Ironside [8], gave admirable reviews of the embryology of these structures and the various anatomical relationships which these neoplasms may show. The present study will confine itself to purely clinical issues, however, and the problems of histological characterization and nomenclature will be avoided by speaking simply of "tumours of the hypophyseal stalk."

The recognition of the existence of a tumour within or above the sella turcica is not difficult. To predict the type of new growth upon clinical grounds is, however, a perplexing problem in differential diagnosis. For this reason this purely clinical study has been undertaken at the suggestion of Dr. Gordon Holmes. The material consists of twenty-one cases of tumour of the hypophyseal stalk. In addition, for the sake of comparison, we have analysed twenty cases of adenoma of the pars anterior of the hypophysis, and nine tumours arising from the lepto-meninges above the sella (suprasellar meningioma or endothelioma). All of these cases have been histologically verified in the laboratory of the National Hospital, Queen Square, by Dr. J. G. Greenfield. The hypophyseal stalk tumours will be described in detail, but the other two groups will be presented only in contrasting tables and discussions.

Martin and Cushing [29] point out that three to eight per cent. of all suprasellar neoplasms are primary gliomas of the optic chiasm or of the intracranial portions of the optic nerves, and that these tumours may at times be difficult to differentiate from tumours of the hypophyseal duct. No similar cases occur in the present series.

Sixteen of the tumours of the hypophyseal duct had arisen from cell-rests of the cranio-pharyngeal duct (Rathke's pouch). Of these, twelve contained adamantinomatous tissue. The other four were of epithelial structure. There were four cholesterin-containing cysts of the infundibulum, in the walls of which too little original tissue remained for diagnosis. Two of these cysts lay in the sella beneath the pituitary body but attached to the stalk itself. Because of their position, it seemed impossible to ascribe to them any origin but a cell-rest of Rathke's pouch. Duffy [18] has described intracystic papillomas, and Cushing has illustrated a similar condition [9]. It is quite possible that at operation soft papillomatous tissue within these cysts may have been broken up by the surgeon's curette and lost in the subsequent aspiration of the cystic contents. The remaining case was a cyst of the infundibulum in which glial and primitive ependymal tissue grew in such a way as to produce a picture which suggested a medullo-epithelioma.

The cases of adenoma of the pars anterior were selected so as to exclude any in which there had been definite signs of acromegaly. Despite this, in a few of them slight suggestions of a fugitive or obsolete hyperfunction had to be recorded. (Cf. Bailey and Cushing [4].)

The material, as summarized in Table I, bears out the well-known fact that adenoma of the pars anterior is almost unknown before the age of 15, and that the suprasellar endothelioma rarely occurs before 30. Cushing [10] and Dott and Bailey [16] have reported the only cases on record of a child younger than 15 with an adenoma of the hypophysis.

Table I.—Age Incidence, according to the Age of Onset of Symptoms.

	Stalk		Adenoma		Endothelioma	
Age incidence	Male	Female	Male	Female	Male	Female
0 to 15 years	4	2	0	0	0	0
16 to 30 ,, ...	1	4	1	3	1	0
31 to 45 ,, ...	3	4	3	6	1	4
46 to 60 ,, ...	3	0	2	5	1	2
Total ..	11	10	6	14	3	6

This difference in age incidence is of great importance, because, as will be shown below, those symptoms which have been regarded as an aid in the differentiation of the stalk tumours from the other two types are found predominantly in children and young adolescents. In older patients the clinical picture of stalk tumours often resembles closely the syndrome of the non-acromegalic pituitary tumour or the endothelioma. Cushing and Eisenhardt [12], in their recent study of the suprasellar meningiomas, have recognized this difficulty.

The age incidence recorded here is consistent with the experience of other authors. In 1922 [9] Cushing tabulated the occurrence of twelve cases under 20, fifteen cases between the ages of 21 and 40, and eight cases between 41 and 60. Again in 1927 [10] he reports the occurrence of eighteen cases under the age of 15, and thirty-four cases thereafter. The earliest onset of symptoms seems to be that reported by Bailey in 1924, [2], whose Case 2 began at the age of 6; or Case 1 of Olivecrona and Lysholm [30], whose symptoms began at 5. The oldest recorded case would seem to be the final one presented here, in whom definite visual disturbances began at the age of 58, after two or three years of very uncertain endocrine disturbances.

The cases are arranged in order according to the age at which the symptoms first appeared.

Case 1.—*Male, aged* 11. *Onset at* 8 *with headaches and vomiting. Periods of amblyopia. Diplopia. Paræsthesiæ and pains in extremities. Irritability. Growth stunted. Visual acuity* $\frac{6}{9}$. *Papillœdema. Normal sella. Possible crossed palsy. Subtentorial decompression. Death. Autopsy: semi-cystic adamantinoma causing generalized internal hydrocephalus and pressure upon the chiasma from above.*

Case 1.[1]—Douglas F., an 11-year-old boy, was admitted on March 15, 1918, to the service of Dr. F. E. Batten. For three years he had been suffering from recurrent periods of headache associated with vomiting. Fifteen months before his admission the severity of these attacks increased, and he complained of severe pain and "pins and needles" in both legs and of periods of misty vision. In the month just before admission vision deteriorated further, diplopia occurred, and he had attacks of momentary loss of strength in both legs. The only mental disturbance was the occurrence of a certain amount of irritability.

In the record the patient is briefly described as small and poorly nourished. His weight, 49 lb., was that of an average 7-year-old boy. Visual acuity was $\frac{6}{9}$ on both sides. Both discs were swollen to 4-5 D. Rough tests revealed no defects in the visual fields. There was a suggestion of weakness on the right side of the tongue and face and on the left half of the body, but with no corresponding disturbance of his reflexes.

---

[1] Critchley and Ironside; Case 4.

The cerebrospinal fluid was normal, containing only five cells per cubic mm. and 20 mg. of protein. The Wassermann reaction was negative in the cerebrospinal fluid, but was weakly positive in 2 c.c. of blood-serum on one occasion. Unfortunately this was never repeated. X-rays revealed no intracranial abnormalities.

On April 3, 1918, a subtentorial decompression was performed, but no tumour was seen. Death occurred twenty days later, after a stormy post-operative course with convulsions and high fever.

At the autopsy a large nodular semi-cystic tumour was found above the sella. The tumour arose from the infundibulum, the upper part of which it entirely replaced. The tumour pushed up the floor of the third ventricle from the tuber cinereum to the corpora mamillaria, so that there was generalized internal hydrocephalus and a pressure cone. It pressed upon the optic chiasma from above and, extending out in front of the chiasma, it exerted pressure upon the gyri recti of the frontal poles. Parts of the mass were cystic, but the major portions were vascular and relatively solid. Histologically, it was a typical adamantinoma.

Case 2.—Female, aged 12. Lifelong mild headaches. Acute onset at 9 with meningitis?, followed by persistent headaches and emaciation. Later obesity, polydipsia, polyphagia and deterioration of vision. Stunted growth. Obese. No sexual development. Severe amblyopia. Optic atrophy. Concentric contraction of fields. X-ray: absorption of posterior clinoids. Second admission: blind, stuporous. Death. Tumour found at autopsy attached to pituitary stalk filling the third ventricle and obstructing the aqueduct. Adamantinoma with large cystic areas.

Case 2.—Alice T., a 12 year-old girl, was admitted to the service of Dr. Gordon Holmes on August 22, 1922. The patient had always suffered from mild headaches. Three years before her admission she had an acute febrile illness, diagnosed "meningitis," in which there was intense occipital headache, pain in the back of the neck, visual difficulty of uncertain nature in the right eye, and diplopia. At a later stage of the illness she had high fever and became unconscious for about ten hours. There was a period of amblyopia so severe that she could not recognize people.

Ever after this illness the child had severe headaches, at first left temporal and later frontal. For two years she was emaciated, but in the year just before she came under observation she became obese and had polydipsia and polyphagia. Presumably there was polyuria, but this was not specifically mentioned.

The patient was of small stature, but weighed 99 lb. Her features and her hands and feet were delicate, but the abdomen and buttocks were large. There was no development of secondary sexual characteristics except a slight amount of axillary hair. Menstruation had not begun.

Vision was reduced to light perception in the right eye, and to $\frac{3}{60}$ in the left. Both discs were pale. The left visual field showed concentric peripheral constriction. There was slight weakness of the external rectus on the right side. The X-rays revealed absorption of the posterior clinoids and an otherwise normal sella turcica.

On September 17 the patient was discharged and was readmitted February 21, 1923. In the interval vision had deteriorated further, headaches and vomiting had become severe, and she had become listless and apathetic.

The patient was now totally blind in the right eye, and could barely count fingers at arm's length with her left. Otherwise her condition was essentially unaltered. The cerebrospinal fluid was examined and was found to be normal in all respects.

She gradually lapsed into a stupor and passed through a period of flexor spasms and postures into a later stage in which extensor reflexes could be elicited by massive stimulation.

On March 3, 1923, she died.

At autopsy the space above the sella was found to be filled by a huge multiloculated cystic tumour about the size of a large walnut. The optic nerves were stretched in front of the tumour and the third nerve appeared behind it. The pituitary body was attached to it by the stalk. The mass was a large triangular structure with its point downwards. This lower point was solid, and in areas almost bony. The upper border of the mass filled the entire area between the genu of the corpus callosum anteriorly and the superior colliculi behind. The cerebral peduncles seemed to be flexed backwards, so that obstruction of the aqueduct was inevitable. The ventricles of the fore-brain were widely dilated. This involvement of the peduncles explains the decerebrate phenomena which occurred before the patient's death.

Histologically, the tissue from the firm area was typically adamantinomatous.

Case 3.—*Male, aged* 10. *Onset at* 10. *Suboccipital pain. Urticaria. Drowsy. Diplopia. Growth stunted. Feminine fat distribution. Visual acuity* $\frac{3}{12}$. *Papillœdema. Bitemporal hemianopia. Enlarged sella. Cystic tumour of stalk found at operation. Death. Adamantinoma.*

Case 3.[1]—Eric H., a 10-year-old boy, was admitted to the service of Dr. Gordon Holmes on October 14, 1921. Four months earlier the patient had complained of pain and stiffness in the back of the neck. One month later headaches began, gradually increasing in severity; and after another month these were associated with vomiting. At about the same time a rash appeared on his body, with lachrymation and a feeling of "hot flushes" and coldness of the hands. Drowsiness and diplopia followed. For some months the patient had seemed to be gaining weight, but no obvious disturbance in water metabolism had been noted.

---

[1] Critchley and Ironside; Case 2.

The patient was 46 in., in height and weighed 54 lb. (An average 7-year-old boy measures 46 in. and weighs about 49 lb.) His features and his hands and feet were delicate. The neck was short and thick, the mammæ prominent, and the suprapubic fat increased. The patient was drowsy and difficult to examine.

Vision was reduced to approximately $\frac{3}{18}$ on both sides. Both discs were swollen 5 D., with distended veins and retinal hæmorrhages. The fields could be outlined only roughly, and showed an indefinite temporal loss. Acetone was present in the urine. The sella was reported to be "greatly enlarged"; and opacities could be seen both within and above it.

On October 18, 1921, Sir Percy Sargent did a right parietal decompression. Exactly one month later he made a left frontal approach to the base, tapping the ventricle and elevating the left frontal pole. A tumour was exposed, bulging around the optic nerve. From the tumour some dark yellow, blood-tinged fluid was aspirated, which proved to contain cholesterin. Fragments of the tumour were removed.

The patient died twenty hours later, without ever fully regaining consciousness.

At autopsy a tumour was found attached to the anterior surface of the upper part of the infundibulum. Except at this point of attachment the tumour was invested by a fibrous capsule. The mass forced the entire floor of the third ventricle upwards, from the lamina terminalis to the mammillary bodies, producing a moderate amount of internal hydrocephalus. The mass had opened the sella from above, enlarging it and flattening the pituitary body. The posterior clinoid processes were forced backwards and were partly absorbed.

The upper part of the mass was fairly solid; but the lower portion was semi-cystic and contained serum, cholesterin and calcareous matter.

Histologically, the tissue was adamantinomatous, in an abundant glial matrix.

Case 4.—Female, aged 12. Onset at 11. Headaches. Pain in shoulder. Dysarthria. "Measles" followed by listlessness. Generalized convulsions with visual aura. Vertigo. Squint and diplopia. Stunted growth. Visual acuity reduced. Papillœdema. Fields generally contracted. External rectus palsies. Possible left hemiparesis. Subtentorial decompression. Death. Adamantinoma found at autopsy.

Case 4.—Youla W., a 12-year-old girl, was admitted to the service of Dr. W. J. Adie on November 23, 1926. The patient had been suffering for one year from bouts of headache (especially over the right eye) which would last twenty-four hours and then terminate in vomiting. After these bouts she would have numbness and pain in the shoulders, and a short period of difficulty in articulation.

Six months before, she had an illness which was called "measles," followed by a definite change in her behaviour, with a tendency to quietness, listlessness, &c.

In the last month she had had a series of four generalized convulsions. These were preceded by an appearance of "dazzling lights"; but these lights had appeared also at other times, possibly in relation to momentary attacks of "giddiness." For a few weeks there had been squint and diplopia.

The patient was described as "infantile" in appearance, with the development of a child of 7. She was mentally alert and cheerful. Her visual acuity was $\frac{6}{36}$ in the right eye, and $\frac{1}{60}$ in the left. Both discs were markedly swollen, with retinal hæmorrhages and engorgement. Both visual fields showed concentric peripheral contraction.

In addition to bilateral external rectus palsies, there was some weakness of the left side of the face and weakness and inco-ordination of the entire left side of the body. The left knee-jerk was exaggerated, and there was an equivocal left plantar response.

On November 30, 1926, Mr. Armour did a subtentorial decompression. The patient died ten hours later.

At autopsy a tumour was found above the sella, pressing the chiasma forward and upward against the frontal lobes. A mid-sagittal section showed the lower part to be fairly solid, with two cysts each about the size of a pigeon's egg. One of these was pressing backwards between the peduncles, and the other upwards into the floor of the third ventricle. The pituitary body was compressed, but otherwise normal. The backward pressure of the posterior cyst blocked the aqueduct and gave rise to a moderate amount of internal hydrocephalus.

Histologically, the lowest pole of the mass was made up of typical adamantinomatous tissue.

Case 5.—*Male, aged* 15. *Onset at* 13. *Lethargy, headache and vomiting. Insomnia, diplopia, conjunctivitis, papillœdema. Period of subsidence of symptoms but for lethargy and under-nourishment. Final recurrence of pressure symptoms. Growth stunted. No sexual development. Visual acuity reduced. Papillœdema. Homonymous field defect. Enlarged sella, absorption of clinoids, opacities above and behind. Unsuccessful attempt to expose tumour. Death. Autopsy: Rathke pouch tumour with areas suggesting adamantinoma.*

Case 5.—Reginald S., a 15-year-old boy, was admitted to the service of Dr. Gordon Holmes on June 7, 1928. Thirteen months before his admission the patient had become lethargic, and had complained of headache and vomiting for a period of approximately three weeks. Three months later he developed insomnia, diplopia and conjunctivitis, and on examination was found to have papillœdema. During the following months he was physically under par, lacking in energy or appetite. Two months before admission there was a relapse, the patient again becoming lethargic, weak and weepy. After a few weeks' sudden bouts of vomiting after meals occurred, at first only in the morning, but later throughout the day. At this time the patient held his head as though in pain.

The patient was undersized, and weighed 69 lb. (the weight of an average 11-year old boy). The genitalia were small and no growth of pubic hair had occurred. Visual acuity was $\frac{6}{18}$ on the right and $\frac{6}{24}$ on the left. Both discs showed about 4 D. of swelling. The right visual field showed a large upper temporal defect, and the left loss of the entire nasal field, sparing macular vision. There was counter-clockwise rotatory nystagmus on looking to the right, and clockwise rotatory nystagmus on looking to the left, and bilateral exophthalmos. The left side of the face lagged in emotional expression.

The cerebrospinal fluid was clear, contained no cells, 10 mg. of protein, and normal amounts of glucose and chlorides.

X-rays of the skull showed an enlarged sella turcica with absorption of the bony processes and irregular opacities behind and to the right of the sella. (Plate VII, fig. 1.)

On June 29, 1928, Sir Percy Sargent made a right temporal approach to the base. Despite a transcallosal ventricular puncture and elevation of the temporal lobe with apparent exposure of the pituitary fossa, no tumour was seen.

The patient died on the day of operation.

At autopsy the skull was found to be thinned, the pituitary fossa was flattened, and an irregular tumour mass was found arising from the infundibulum, and filling the space from the peduncles behind to the chiasma in front, but with little or no distortion of either. A large thin-walled cyst, containing greenish fluid, was found pressing upwards against the floor of the third ventricle.

Histologically, the tissues of the more solid lower pole of the cyst proved to be those of a typical Rathke pouch tumour, with areas suggesting an adamantinoma, set in a neuroglial matrix with small foci of collagenous, cartilaginous, calcareous and myxomatous degeneration and epithelial whorls.

Case 6.—*Male, aged* 14. *Onset at* 14. *Headache, amblyopia and vertigo in bouts. One period of unconsciousness followed by somnolence and generalized pains. Growth stunted. No sexual development. Obesity of feminine type. Genital aplasia. Visual acuity much reduced. Optic atrophy. Predominantly inferior homonymous defects in the visual field. Small sella. Inoperable stalk tumour found at operation. Death. Autopsy. Adamantinoma.*

Case 6.—James T., a 14-year-old boy, was admitted to the St. Thomas's Hospital on July 26, 1927, but was discharged on August 17. Again on September 18 he was readmitted, this time on the service of Sir Percy Sargent.

In May, five months before his second admission, the patient had begun to suffer from recurrent attacks of headache and amblyopia, associated with giddiness. These attacks occurred about every second day, and sometimes seemed to be precipitated by bright light. The headache usually began in the vertex, less commonly in the occiput, and occasionally the pain radiated to the frontal region or behind the ears. Three months after these symptoms made their appearance, during one such bout of pain, the patient lost consciousness. After this he became increasingly somnolent, and had pain in the chest, abdomen and knees. One year before the development of this condition he had had an attack of herpes on the right side of the face with hearing impaired in the right ear.

On examination the patient was found to be infantile and obese, with large rounded breasts and fat pads over the abdomen, thighs and buttocks. There was no axillary or pubic hair; and the external genitalia were minute in size. Visual acuity was reduced to $\frac{6}{60}$ on both sides. Both discs were pale. In the right eye there was a loss of the inferior quadrants, more complete in the temporal than in the nasal field. In the left eye there was a loss of the entire nasal field, and a relative loss of the inferior temporal quadrant.

X-rays revealed a small sella turcica with the anterior clinoids apparently turned in.

The sugar-tolerance curve showed: resting, 0·137; half-hour, 0·175; one hour, 0·193; one and a half hours, 0·112.

The Wassermann reaction was negative in the blood and spinal fluid.

On November 3, 1927, Sir Percy Sargent made a right frontal approach. On the tense dura over the frontal lobe he found a small patch of venous hemangioma. On elevating the lobe the optic chiasma could be seen raised and pushed forward by a large white tumour which lay in the mid-line above the sella, and which pushed out rather more to the left than to the right. The tumour was inoperable. The patient died one hour later.

At autopsy the infundibulum was found to be continuous with a large irregular suprapituitary cyst which occupied the suprasellar space and extended backwards under the crura and adjacent to the pons. The pituitary body was normal in size, but owing to the pressure from above had been pushed right through the floor of the sella. There was a persistent thymus which weighed 66 grm., a small thyroid weighing 17 grm., and markedly hypoplastic testes.

Histologically, the tumour was an adamantinoma.

Case 7.—*Female, aged* 18. *Onset at* 16. *Never menstruated. Headache and vomiting. Amblyopia. Bitemporal hemianopia. Mild uncinate attacks. Lethargy. Growth arrested. Adiposity. Scanty hair. Somnolence and "Witzelsucht." Visual acuity reduced to light perception. Optic atrophy. Sella enlarged. Large cyst found above the pituitary on operation. Death. Autopsy; cholesterin-containing cyst filling the sella turcica below the hypophysis.*

Case 7.—Winifred L., a single woman, aged 18, was admitted to the service of Sir Farquhar Buzzard on February 12, 1920. The patient had always been obese and had never menstruated. For two years she had had intense frontal headache, especially over the left eye. This pain was throbbing and intermittent, and usually at its worst in the morning. For one year vomiting had been associated with these headaches. Two months after the onset of these symptoms vision became blurred, and almost from the start she noted that she could not see objects "from the sides." Examination at that time revealed the presence of optic atrophy.

Shortly before admission she became lethargic and had vague attacks of faintness associated with an unpleasant taste. During the two years of her illness there had been no growth in stature, and there was an impression that she had gained weight, chiefly in the hands and face.

The patient is described as infantile in appearance, voice and manner—resembling a girl of 14. She weighed 104 lb. Her adiposity was marked, especially in the upper arms, abdomen and axillary girdle. The hair was scanty in the axillæ and pubes. The patient was somnolent with occasional restlessness and "Witzelsucht."

Visual acuity was reduced to light perception. Both discs were atrophic. No visual fields were obtainable.

The blood-pressure was 100/70. The cerebrospinal fluid contained no cells, 0·025 mg. protein, 0·033 mg. glucose. The Wassermann reaction was negative.

No glycosuria occurred after the ingestion of 100 grm. of glucose.

The X-ray revealed a greatly enlarged sella turcica.

On March 20, 1920, Sir Percy Sargent made a right fronto-temporal approach. On elevation of the frontal pole a large fluctuant cyst was exposed in the pituitary region, with the optic nerve lying flattened over it. The cyst was incised and 20 c.c of amber-coloured fluid containing cholesterin crystals were aspirated.

After the operation the patient became delirious and incontinent, with a fever that rose to 106° F., and attacks of urticaria and œdema. On April 2 she died.

At autopsy a large cystic tumour was found filling the sella turcica, with the optic chiasma and nerves lying flattened above it, extending from the peduncles behind to the lamina terminalis anteriorly, and slightly elevating the floor of the third ventricle. The cyst was filled with brownish fluid containing numerous plate-like cholesterin crystals and some large solid masses. One plate of calcareous matter was adherent to the upper wall of the cyst.

Histologically, the wall of the cyst consisted solely of fibrous tissue, blood-vessels and chronic inflammatory infiltration. (Cf. Case 19, fig. 1, p. 149.)

Case 8.—*Female, aged* 21. *Single. Onset at* 17. *No menstruation. Headache, nausea and vomiting. Retro-orbital pain. Lachrymation. Amblyopia. Possible polydipsia. Growth adolescent. Breasts undeveloped. Little pubic hair. Visual acuity much reduced. Nasal pallor of discs. Bitemporal hemianopia. Sella poorly defined. Operation exposed tumour arising from fossa. Death. Autopsy: adamantinoma.*

Case 8.—Eileen R., a 21-year-old unmarried woman, was admitted to the service of Dr. Gordon Holmes on November 30, 1926. The patient had never menstruated. Four or five years before coming to the hospital she had complained of occasional bouts of nausea and vomiting associated with frontal headaches. These would last from one to three days. Two years before her admission she had suffered from retro-orbital pain on reading, with burning and lachrymation. Then her vision began to blur, the letters jumping and scintillating. Her right eye was more affected than her left at this time. After one year there had been rapid deterioration of vision, with total inability to read for at least six months. Dull aching headaches, either diffuse or centring in the left temporal region, occurred during the last few months, and recently she had had an uncertain amount of polydipsia.

The patient is described as small of stature and infantile in form, with undeveloped breasts and delicate hands and feet. Pubic hair was sparse. Visual acuity was $\frac{6}{60}$ in the right eye and $\frac{3}{36}$ in the left. Both discs showed marked pallor of the nasal margins. The visual fields showed a bitemporal hemianopia.

The X-ray of the skull revealed no abnormality of the sella, although the fossa itself was poorly defined. Blood-pressure was 100/78.

On March 12, 1926, Sir Percy Sargent made a right frontal approach and exposed a bluish tumour arising from the pituitary fossa. This was incised and the aspirated fluid and debris were found to contain cholesterin crystals.

On March 15 the patient died.

At autopsy a tumour was found lying in the suprasellar space and stretching forward over the pituitary fossa and under the optic chiasma. In front of the chiasma the mass projected upwards between the frontal lobes. Behind the chiasma it pressed upwards against the floor of the third ventricle. The stalk of the pituitary emerged from the under-side of the mass.

Grossly, many minute cysts containing gelatinous material could be seen. Histologically the tissues were adamantinomatous.

Case 9.—*Female, aged* 27. *Single. Onset at* 17. *Amenorrhœa. Progressive amblyopia. Obesity. Headaches. Loss of hair. Drowsiness. Disturbance of memory. Growth adolescent. Adipose. Body hair absent. Visual acuity markedly reduced. Optic atrophy. Bitemporal hemianopia with loss of both inferior nasal fields. Operation followed by death. Autopsy: adamantinoma, intrasellar.*

Case 9.—Louisa N., a 27-year-old single woman, was admitted to the service of Dr. Adie on December 1, 1925. At 17 menstruation had ceased. At about the same time her vision became dim, first in the right eye with subsequent slight improvement, and then with a progressive deterioration affecting both eyes, but with the left eye deteriorating more rapidly than the right. Diplopia occurred early in the development of the visual defects. For one year there had been much gain in weight and headaches had increased in severity. These were localized behind the eyes, and were described as "boring," and as going into the head and across the forehead. Vomiting was sometimes associated with these pains. Recently there had been loss of hair, marked drowsiness and a disturbance of memory.

The patient is described as "infantile" in appearance, with delicate features and tapering but stout hands. She was obese, weighing 130 lb. Her skin was smooth, dry and "doughy." Her eyebrows were scanty, and there was no axillary or pubic hair. Visual acuity was diminished to counting fingers. The discs were pale, the edges clear. The visual field of the right eye showed complete loss of the temporal and inferior nasal portions, with relative sparing of central vision. The visual field of the left eye was completely obliterated except for a small island in the upper nasal field adjacent to the fixation point.

The sugar-tolerance curve, following the administration of 50 grm. of glucose, was as follows: resting 0·076; half-hour, 0·148; one hour, 0·172; two hours, 0·110.

Blood-count: red blood-corpuscles, 3,720,000; hæmoglobin, 100 per cent., colour index, 1·2; slight poikilocytosis; white blood-corpuscles, 6,100; lymphocytes, 54 per cent.; eosinophiles, 5 per cent.

The patient was operated upon but the operative record has been lost. Shortly after the operation the patient died.

At autopsy a large thick-walled cyst was found filling the sella turcica which, in turn, was much enlarged. The posterior clinoids were completely absorbed. The cyst pressed upwards into the floor of the third ventricle between the optic chiasma and the infundibular recess.

Histologically the cyst wall was adamantinomatous.

Case 10.—*Female, aged* 19, *Single. Never menstruated. Onset at* 18. *Obesity. Polyuria. Amblyopia. Headache and drowsiness. Stunting with lack of sexual development. Scanty body hair. Visual acuity markedly reduced. Optic atrophy. Temporal hemianopia. Sella enlarged, erosion of clinoids. Intrasellar opacities. Operation disclosed a cystic tumour of the stalk which was drained. Convulsions. Improvement.*

Case 10.—Catherine C., a single woman of 19, was admitted to the service of Dr. George Riddoch on April 24, 1928. When she was 2½ years old she had had an illness which had been called "meningitis." About this illness no details were known. The patient had never menstruated and her breasts had never developed. During the year before entering the hospital there had been marked gain in weight and polyuria. (No specific mention of polydipsia is made.) For three months vision had been failing, showing itself chiefly as a difficulty in distinguishing colours. Sharp and severe frontal headaches had developed in the same period, and some accompanying drowsiness.

On examination the patient was found to be small and obese, weighing 125 lb. The excess fat was chiefly abdominal and suprapubic. The breasts were poorly developed and the pubic hair was scanty. Visual acuity was reduced to light perception in the right eye and to $\frac{6}{36}$ in the left. The disc on the right was yellowish-white throughout, and the left showed temporal pallor. The right field could not be outlined; in the left there was a temporal loss with some constriction of the nasal field.

The sugar-tolerance curve was as follows: resting, 0·110; one hour, 0·197; two and a half hours, 0·190. There was a trace of sugar in the urine.

X-ray showed enlargement of the sella turcica, with erosion of the posterior wall and some absorption of the posterior clinoids, and intrasellar opacities. (See Plate VII, fig. 2.)

On May 11, 1928, Sir Percy Sargent made a frontal approach, exposing a cystic tumour over which the optic nerve was stretched. The tumour was incised and three ounces of dark, greenish, cholesterin-containing fluid was aspirated. Six days later the patient had a series of convulsions.

On May 23 the right eye had light perception and the left eye had improved to $\frac{6}{9}$ acuity, with general improvement of the visual field. Shortly thereafter the patient was discharged from the hospital.

In April, 1929, she presented herself for re-examination. After the operation her obesity increased, and menstruation never occurred. Vision in the right eye rapidly deteriorated, but improved steadily in the left. She has had no headaches.

Her height was 5 ft. 3½ in. Her weight was 158 lb., an increase of nearly 35 lb. in the twelve months since her admission. The breasts were underdeveloped with very little glandular tissue. Hair over the trunk was fine and sparse, except in the axillæ where it was fairly abundant. The skin was dry and thin. The right eye bulged slightly and was totally blind. Acuity was $\frac{6}{6}$ in the left eye. There was bilateral optic atrophy, much more marked on the right than on the left, however. In the visual field of the right eye there was an upper temporal quadrant defect for all sizes of test objects and both for red and white.

Case 11.—*Male, aged* 27. *Married. Onset at* 22. "*Influenza,*" *followed by headaches, amblyopia, obesity, loss of libido, genital aplasia. Somnolence, polyuria and polydipsia. Short delirium. Obesity of feminine distribution. Genital atrophy. Loss of body hair. Visual acuity reduced. Optic atrophy. Right hemiparesis. Enlarged sella. Unsuccessful attempt to expose tumour. Death. Cholesterin-containing cyst of infundibulum.*

Case 11.—Ben F., a 27-year-old married man, was admitted to the service of Dr. Gordon Holmes on October 15, 1923. Five years before he had had an illness of uncertain nature which had been called "influenza of the head type," and thereafter the patient had complained of headaches and dim vision, of progressive gain in weight, of loss of all libido and genital atrophy. For one year there had been a sharp increase in the severity of the headaches, accompanied by marked somnolence, polyuria, polydipsia and attacks of vertigo. For a few months the patient had apparently been intermittently delirious, with thick speech, hiccoughing and sighing, labile emotions, fluctuating clarity and confusion.

Examination revealed an obese man, with over-developed mammæ, broad hips and a prominent suprapubic pad of fat. His skin was soft and pale. His hair, although abundant on head and eyebrows, was sparse over the rest of his face and in the axillæ and pubic region, and entirely absent from the trunk and extremities. The pubic hair had a transverse upper margin. The penis and scrotum were small; the left testis was small and the right could not be felt in the scrotum. Examination was difficult in the face of the patient's dullness and apathy. Response to questions was limited. He tended to stare dully or to weep. Visual acuity was approximately $\frac{6}{24}$ in both eyes. Rough tests revealed no visual field defects. Both discs were pale, perhaps more strikingly so on the nasal than on the temporal margins. There was weakness of the right sides of the face and tongue, weakness and awkwardness of the right arm and leg, and exaggeration of the deep reflexes on the right side, with an extensor plantar response on the right.

X-ray revealed an enlarged and irregular sella turcica.

The sugar-tolerance curve, after the ingestion of 50 grm. of glucose, was as follows: resting, 0·170; half hour, 0·231; one and a half hours, 0·176.

His urine was of consistently low specific gravity, varying from 1·005 to 1·010. No measurements of quantity were made.

On November 16, 1923, Sir Percy Sargent made an attempt to expose the pituitary fossa, which failed because of the increased intracranial pressure. Two days later the patient died.

At autopsy the infundibulum was found to be converted into a cyst which contained yellow fluid and cholesterin. The chiasma was greatly thinned and lay between the cyst above and a somewhat enlarged pituitary body below. The cyst filled the space above the sella, slightly elevating the floor of the third ventricle.

In the cyst wall nothing was found on histological examination except fibrous tissue and hæmorrhages.

Case 12—*Female, aged* 34. *Single. Onset at* 32. *Headaches. Loss of hair. Gain in weight. Amblyopia. Somnolence. Polyuria and polydipsia. Marked obesity. Visual acuity markedly reduced. Optic atrophy; in the right eye temporal hemianopia. Left eye: preservation of central band only. Left hemiparesis. Operation exposed cystic tumour of infundibulum. Drained. Improvement. Tissue largely adamantinomatous.*

Case 12.—Annie T., a 34-year-old single woman, was admitted to the service of Dr. Gordon Holmes on June 30, 1927. Two years before this the patient began to suffer from headaches of increasing severity. These headaches were sometimes general, but more often were localized in the left frontal or left occipital regions, with periods of extreme tenderness and soreness in the left occiput. At the same time she noticed a loss of hair and the onset of a period of progressive gain in weight, in the course of which she increased from 126 to 200 lb. A few weeks after these symptoms were noted her periods, which for two years had been excessively profuse, suddenly stopped. Two months later there was disturbance of vision, first in the left eye and then after a few weeks in the right. In each eye blurring after reading was noted first, then a noticeable dropping out of the temporal field, and finally, in about six months, a deterioration almost to blindness. One year before her admission the patient began to show somnolence, which in the final months became very marked. In the weeks just before coming under observation there was polyuria and polydipsia, some disturbance of gait and vague mental confusion and difficulty in memory.

On examination the patient was found to be very obese, weighing 200 lb., with pads of fat over the neck and breasts. The adipose tissue was slightly tender on palpation. Her limbs were disproportionately short and slender, and her hands small. Axillary hair was abundant, but the pubic hair was scanty. The patient was somewhat somnolent and restless and when roused she was confused. Visual acuity was $\frac{1}{60}$ in the right eye and $\frac{1}{60}$ in the left. The fundi showed temporal pallor, more marked in the left eye than in the right. The right field showed a complete temporal loss, and vision in the left eye was limited to a narrow horizontal band of central vision, extending from 10° nasally to 20° temporally. There was left-sided weakness and inco-ordination, with exaggerated deep reflexes on the same side, absent left abdominal reflexes, and an extensor plantar response from the left sole.

X-ray of the skull revealed no abnormalities.

The sugar-tolerance curve was as follows: resting, 0·101; half-hour, 0·213; two and a half hours, 0·090.

On July 1, 1927, Sir Percy Sargent made a right frontal approach, exposing a large cystic mass above and behind the right optic nerve. Small masses of solid tumour were removed and the cystic fluid aspirated.

The tumour was obviously a Rathke pouch derivative. It was composed of a stroma of dense fibrous connective tissue, and cellular trabeculæ with a covering of cuboidal epithelium resembling an adamantinoma.

On July 24 visual acuity in the right eye was $\frac{6}{60}$, and in the left there was light perception only. The right field showed a complete temporal loss, with sparing of temporal vision. The patient was allowed to go home soon after this. No information was obtainable as to the subsequent progress of her illness, except that she died in May, 1928. No post-mortem examination was made.

Case 13.—*Female, aged* 35. *Single. Onset at* 32. *Headache. Lassitude. Increasing apathy. Amenorrhœa. Somnolence. Amblyopia. Final exacerbation of headache and vomiting. Papillœdema of low degree and recent. Homonymous hemianopia. Left hemiparesis. Operation failed to disclose tumour. Death. Autopsy: cystic tumour of infundibulum. "Squamous, prickle-cell epithelioma."*

Case 13.—Dorothy B., a 35-year-old single woman, was admitted to the service of Dr. F. M. R. Walshe on June 17, 1926. The patient had always been "sickly." Three years before admission she developed marked lassitude, and occipital headaches which radiated to the right side and which were at times associated with burning sensations over the same area. She became increasingly weak and dull, and menstruation ceased. No further developments were recorded until four months before her admission, at which time there was marked somnolence, unsteadiness of gait so that she often fell, weakness of the right hand and dimness of vision. For two weeks she had been bedridden, extremely drowsy, her speech thick, and she suffered from headache and vomiting.

The patient, on examination, was found to be somnolent but she could be roused. Her speech was thick. The record contains no description of body form and no record of visual acuity. Both discs were swollen to about 2 D. The fields showed a right homonymous hemianopic loss. Neither pupil reacted to light. The reaction to convergence was limited on the left, but the left eye converged poorly. The left arm was weak and deep reflexes were increased in the left arm and leg. Abdominal reflexes were elicited from neither side, and there were bilateral extensor plantar responses.

The Wassermann reaction was negative in blood and spinal fluid. X-ray examination revealed no abnormality of the pituitary fossa.

Sugar-tolerance: resting, 0·110; one hour, 0·300; two hours, 0·120.

On June 26, 1926, Mr. Armour made a right frontal approach to the base, but no tumour could be seen. During the next two months the patient became increasingly somnolent, with palatal speech, absent pharyngeal reflexes, rigid neck, trismus, spastic legs, absent abdominal reflexes and bilateral extensor plantar responses. On August 13 the patient died.

At autopsy a mass was found which consisted of a firm, white, gritty anterior portion, and two cysts posteriorly. The firm portion lay above the sella turcica, pressing downwards into it, and raising the optic chiasma up and forwards. One cyst, about the size of a walnut, pressed backwards into the upper end of the cerebral peduncles. The other cyst pressed upwards into the floor of the third ventricle.

Histologically, the tumour consisted of thick trabeculæ of "prickle cells," corresponding to a squamous-celled epithelioma of the naso-pharynx.

Case 14. *Female, aged 35. Single. Onset at 32. Amblyopia. Headaches. Obesity. Amenorrhœa. Diplopia. Photophobia. Bitemporal visual loss. Occasional vomiting and polyuria. Obese. Marked loss of visual acuity. Questionable haziness of upper disc margins. Bitemporal paracentral scotoma. Unsuccessful attempt to expose sella at operation. Death. Autopsy: adamantinoma.*

Case 14[1].—Florence S., a single woman of 35, was admitted to the service of Dr. Gordon Holmes on November 29, 1919. Three years before this she complained of visual fatigue on reading. Nothing further occurred for two years. Then, a year before coming under observation, she developed bilateral retro-orbital pain which radiated to the vertex and to the back of the neck. At the same time she began to gain in weight (increasing from 154 to 230 lb. in twelve months). At the same time her periods ceased and there was a question of loss of hair. For seven months vision had been blurred and indistinct, with occasional diplopia. In the month before entering the hospital there was photophobia and a definite loss of acuity in both temporal fields, occasional vomiting, and polyuria.

---

[1] Critchley and Ironside; Case 3.

Examination revealed an obese woman, measuring 5 ft. $5\frac{1}{2}$ in. and weighing 217 lb. The adiposity was uniformly distributed. Body hair was sparse. On the right visual acuity was less than $\frac{6}{60}$ and on the left was $\frac{6}{60}$. The discs showed slight haziness of the upper margins, and possibly slight swelling. The visual fields were evidently difficult to outline and the data were somewhat confused. It was probable, however, that in both eyes there were large paracentral scotomata lying to the temporal side of the fixation point, and in the right eye including the fixation area more completely than in the left. On the right there was an external rectus palsy.

On ingesting 175 grm. of glucose there was glycosuria after two hours, which disappeared one and a half hours later. The specific gravity of the urine varied from 1·008 to 1·030.

X-rays seemed to reveal no enlargement of the sella in the antero-posterior plane, but a lateral dilatation.

On January 24, 1920, Sir Percy Sargent did a right temporo-parietal decompression, but was unable to expose the sella.

On February 28, during a second attempt to expose the sella, the patient died.

At autopsy a semi-cystic tumour was found in and above the sella turcica. It was slightly to the left of the mid-line and lay behind the optic chiasma, pushing it forward. There was some internal hydrocephalus with wide, flattened convolutions and a terminal pressure cone. The sella was broad, deep and considerably enlarged, chiefly at the expense of the anterior margins. The posterior clinoids were pushed backwards. The tumour appeared to have grown largely from beneath the anterior lobe of the pituitary body, spreading upwards, obliterating the infundibulum and invaginating the floor of the third ventricle so as to press upwards and backwards between the optic thalami.

Much of the tumour was solid, but in the upper portion were cysts which contained yellow fluid.

Histologically the tissue was a primitive type of adamantinoma.

Case 15.—*Male, aged* 36. *Married. Onset at* 34. *Amblyopia. Headache. Vomiting. Vertigo. Gain in weight. Loss of pubic hair. Loss of libido. Feminine habitus. Genitalia small. Hair scanty. Visual acuity reduced. Fundi normal. Bitemporal hemianopia. Operation exposed cystic tumour of stalk. Death. Autopsy: hypophyseal duct epithelioma.*

Case 15.—Ewart M., a married man, aged 36, was admitted to the service of Dr. Gordon Holmes on February 10, 1927. Two years before he had suddenly noted dimness of vision, which on examination proved to be due to bilateral relative central scotoma. The visual difficulty was slowly progressive, and spread over the entire field of vision. A few months after the onset the patient began to suffer from bouts of headache, which were at first both occipital and frontal, but which later became exclusively frontal. These bouts were at times precipitated by sudden jarring or sudden movement. Later they came to be associated with vomiting and vague giddiness. Coincident with the onset of the headache the patient began to gain weight and to lose pubic hair. One year before admission he noticed loss of libido and gradually, during the ensuing months, a total loss of sexual power. Six months before admission his frontal headaches increased in severity, and he suffered from intermittent bouts of diplopia which seemed to occur equally on looking in any direction.

The patient weighed 134 lb. His pelvis was "somewhat feminine" His genitalia were small. His hair was scanty and fine in the axillæ and pubic region, and quite absent from the trunk or limbs. His skin was soft and "feminine."

Visual acuity in the right eye was $\frac{6}{36}$, and $\frac{6}{12}$ in the left. Neither fundus appeared to be abnormal. In the right eye there was an upper temporal quadrantic defect, while in the left eye there was complete temporal hemianopia. All deep reflexes were exaggerated and there were bilateral extensor plantar responses.

The systolic blood-pressure was 124.

The sugar-tolerance curve: resting, 0·111; half-hour, 0·178; two and a half hours, 0·083.

X-ray showed a very small, shallow sella with complete absorption of both anterior and posterior clinoids. (Plate VIII, fig. 9.)

On February 25, 1927, Sir Percy Sargent made a right frontal approach. A lumbar puncture became necessary to reduce the intracranial pressure. After this a cyst was exposed lying medial to the optic nerve, and on incision about two drachms of yellow fluid were aspirated. Above the cyst a solid tumour could be seen.

The cerebrospinal fluid removed at operation was slightly yellow, with a fine coagulum, and contained fifteen cells, of which 10 per cent. were polymorphonuclear leucocytes and 10 per cent. large mononuclears, and the rest small lymphocytic forms. Total protein was 100 mg. per 100 c.c. and the Pandy was 2 plus. Glucose, 75 mg. per 100 c.c.

The patient died on March 7, 1927, and at post-mortem it was found that a small cystic tumour of the infundibulum lay above the sella, pressing upon the right side of the optic chiasma and pushing the right optic nerve to the left. The cyst contained orange-coloured granular material.

Histologically, there were vascular strands of connective tissue covered by several layers of polygonal epithelial cells, representing transitional epithelium. In the interstices were many mononuclear cells, some of them fat-laden, some lymphocytes. The tumour was evidently an epithelioma of the hypophyseal duct but not an adamantinoma.

Case 16.—*Female, aged 43. Single. Onset at 37 with "influenza" followed by obesity, lachrymation, amblyopia. Headache. Insomnia. Obesity. Anosmia. Visual acuity reduced. Optic atrophy. Predominantly bitemporal field defects. Sella turcica enlarged. Tumour of infundibulum exposed at operation. Incised and aspirated. Survival and improvement. Tissues: complex adenomatous derivative of Rathke's pouch, with some predominantly glial areas.*

Case 16.—Nellie S., a single woman aged 43, was admitted to the service of Dr. Gordon Holmes on June 27, 1924. Eight years before she had been hit on the head, the blow resulting in a cut which required several stitches. There was no evidence of intracranial injury. Two years after this accident she had an undescribed illness called "influenza," and from that time on gained steadily in weight. Three years before coming to the hospital she had complained of excessive lachrymation on using her eyes. This seemed to be relieved by glasses, however, and it was not until eighteen months later that outspoken visual disturbances occurred. At this time she found herself unable to read at all with the unaided right eye, and print remained blurred even with both eyes in use. There was definite loss of the temporal field of the left eye. At this time headaches began to occur frequently. These were usually left frontal, but sometimes right parietal and occasionally suboccipital. The pain was dull but lasted two or three days, preventing sleep, and after some months there was concomitant nausea and retching, but no outspoken vomiting. For six months there had been insomnia.

The patient is described as diffusely obese, weighing 150 lb. She had a small amount of hair on her upper lip and chin. There was no outspoken evidence of dyspituitarism. In the right nostril she failed to recognize camphor, cloves or peppermint, all of which were accurately perceived on the left side. Her visual acuity on the right was $\frac{3}{60}$, and on the left varied between $\frac{6}{36}$ and $\frac{6}{60}$. Both discs presented an unusual anomaly, i.e., a white crescent that swung around from the nasal to the inferior margins. The right disc was otherwise of good colour, but the left disc was grey and atrophic. The visual field of the left eye showed a temporal loss that extended exactly to the mid-line. In the right eye there was a slight general constriction of the temporal margin with relative dimness throughout the whole temporal field, a V-shaped upper temporal notch, and a scotomatous area of uncertain extent lying to the temporal side of the fixation point and probably to some degree including it.

An X-ray showed an enlarged pituitary fossa with absorption of posterior clinoids.

The blood-pressure was 150/112. The sugar-tolerance curve: resting, 0·180; one hour, 0·260; one and a half hours, 0·200.

On July 25, 1924, Sir Percy Sargent made a left frontal approach. The optic nerve could be seen lying flattened out over a mass which seemed to bulge from the region of the pituitary fossa. This mass was incised and aspirated.

Histologically the tissues removed at operation were of two kinds:—

(a) Areas resembling the pars posterior of the hypophysis, and containing definite glial tissue with a tendency to develop long fibres like those of a neurofibroma;

(b) Areas composed of small rounded or goblet-shaped cells with round nuclei, grouped around blood-vessels in irregular acinar formations. Some of these acini contained colloid.

Following the operation the left visual field became further constricted, the left eye finally becoming quite blind, while the right eye improved, but atrophy became more marked in both discs.

After a few weeks the patient was allowed to return to her home.

In April, 1929, the patient presented herself for re-examination, in response to a request. She reported that two years after her operation menstruation had recommenced, occurring thereafter at intervals of four to six weeks, with a rather profuse flow. She felt that she was rather easily fatigued, but that her general condition was stationary except that within the last few months she had been troubled by pain behind the left eye.

Visual acuity in the left eye was limited to light perception, in the right eye was $\frac{1}{18}$. The discs were greyish white, the edges of the left disc somewhat hazy. In the field of the left eye vision was preserved in a small nasal area only; the right field showed general constriction with a deep defect in the upper temporal quadrant. There was a slight divergent squint of the left eye. Otherwise the patient was normal.

Case 17.—*Male, aged* 43. *Single. Onset at* 42. *Orbital pain. Amblyopia. Increasing headaches. Obesity. Scanty hair. Small genitalia. Visual acuity slightly reduced. Normal fundi. Bitemporal field loss. Cystic tumour of the stalk exposed, contents aspirated. Slow recovery with irritative meningitis and Korsakow delirium. Survival with improvement.*

Case 17.—Walter A., a single man aged 43, was admitted to the service of Dr. Gordon Holmes on October 24, 1928. Six months before this the patient had complained of pain and a sense of pressure in the left eye. For two months this was relieved by glasses. Then he noted that vision in this eye was blurred, especially in the outer corner. Gradually the dimness "moved across like a shutter from the left," obscuring more and more of the field. Just one month before his admission he noticed that his right eye fatigued easily, that his vision blurred on reading, and he began to suffer from momentary lancinating pains in the right forehead, vertex and occiput. These became severe enough to make opiates necessary. No definite evidence of metabolic or endocrine disturbance could be secured, but the patient had a somewhat weak and insecure personality and had always depended greatly upon his mother and sister. His own inclination, at first, was to attribute all of his illness to his emotional upset over the death of his mother, which had occurred a few weeks before his first symptoms appeared.

The patient was an obese man, measuring 5 ft. 6 in. and weighing 186 lb.

There was nothing characteristic in the fat distribution. His trunk was sleek and hairless. Axillary hair was scanty and the pubic hair had a horizontal upper margin. The hands were somewhat broad and spatulate. The external genitalia were perhaps small. Visual acuity on the right was $\frac{6}{9}$ and on the left was $\frac{6}{18}$. The eye-grounds were normal. The right visual fields showed slight temporal constriction with a deep wedge-shaped defect in the upper temporal quadrant. In both eyes red could be recognized only in the nasal field. The left visual field showed marked temporal constriction, with a paracentral scotoma lying to the temporal side of the fixation point and including it. There was a deep wedge-shaped sector defect in the upper temporal field.

The blood-pressure varied between 180/110 to 160/90.

X-ray examination showed an irregularly enlarged sella, especially posteriorly, with absorption of the posterior clinoids, and opacities within the sella. (Plate VII, fig. 3.)

On November 2, 1928, Sir Percy Sargent made a right frontal approach. Elevation of the frontal lobe exposed the dorsum sellæ which was bulging only slightly. On incision small masses of gelatinous material, some of it calcified, were removed. The cavity of the sella was found to be greatly enlarged on the left and less so on the right.

Histologically, the tissues removed at operation consisted of a neuroglial network with strands of collagenous connective tissue, spicules of bone, knots of small cells and epithelial elements.

The post-operative course was complicated for many days by a persistent bronchitis with fever, a stiff neck, and lancinating pains from the suboccipital region down the spine associated with myoclonic spasms. There was a group of five generalized convulsions. Repeated lumbar punctures yielded cloudy yellow fluid, containing fresh blood, hæmoglobin, blood-pigments, fibrin, and about 1,000 cells, of which 10 per cent. were polymorphonuclear leucocytes, and the rest small mononuclears. Cultures were consistently sterile.

During this period the patient drifted into a typical Korsakow delirium with characteristic nocturnal exacerbations. Two months later he still showed residual retention difficulties and a slight tendency to confabulation. When examined one month after leaving the hospital it was found that he had acquired a retro-active amnesia for the entire period of his mother's illness and death, his own illness and the operation.

His blood-pressure dropped after the operation to 118/70. Visual acuity on discharge, January 9, 1929, was $\frac{6}{12}$ in the right eye and $\frac{6}{18}$ in the left. Both fields were normal with complete recovery of the red fields. The scotomatous areas and the upper temporal defects had quite disappeared.

An X-ray of the skull at this time showed a large, densely-calcified shadow lying within, above and to the right of the sella. This mass was larger and denser than any that had been seen before operation. One month later, however, upon his return for re-examination, this shadow was remarkably reduced in size. (Plate VII, figs. 4 and 5.)

In April, 1929, five months after his operation, the patient was suffering again from pain, and there was a bitemporal hemianopia with defective macular vision in both eyes, with diplopia as a result. X-rays which were taken at this time showed a vague but extensive suprasellar mass which was so slightly calcified that it could just barely be outlined in the accompanying sketch. (Plate VII, fig. 6.)

Case 18.—*Male, aged* 44. *Married. Onset at* 43. *Unilateral blindness. Retro-orbital pain. Loss of libido. Obese. Scanty body hair. Normal genitalia. Right eye blind. Left acuity* $\frac{6}{6}$. *Temporal pallor. Temporal hemianopia. Sella normal. Cystic tumour of the stalk found on operation. Aspirated. Death. Autopsy: adamantinoma.*

Case 18.—Harry W., a 44-year-old married man, was admitted to the service of Dr. Gordon Holmes on January 20, 1927. Five months before admission he found that he was having difficulty in placing figures in columns. Two months later he was completely blind in the right eye. A few weeks after this he had attacks of transient retro-orbital pain, unassociated with generalized headache or vomiting. At about the same time the vision of the left eye became dim, and he noted loss of the temporal field. For nine months there had been complete absence of libido. During the course of his illness he had gained 5 lb.

Examination showed the patient to be somewhat obese, weighing 182 lb. Axillary and pubic hair was scanty. The genitalia were normal in appearance. He was totally blind in the right eye. Visual acuity of the left was $\frac{6}{6}$. Both discs showed temporal pallor, more marked, however, on the right. There was a complete temporal hemianopia of the left field.

X-ray of the skull showed complete absorption of both the anterior and posterior clinoids with no deformation of the sella itself.

On February 9, 1927, Sir Percy Sargent found a tumour the size of a walnut projecting in front and to the right of the chiasma. The right optic nerve was divided, and the tumour incised and aspirated.

The patient died a few hours later.

At autopsy the sella was found to be rather wide and flat. The tumour lay above the sella, pressing forward between the frontal lobes and upward into the floor of the third ventricle. The right half of the chiasma and the right optic nerve had been destroyed by pressure. The infundibulum emerged from the left side of the tumour.

Section showed the tumour growing into the third ventricle between the mammillary bodies and chiasma up to the middle commissure. It consisted of multiple small cysts, containing green gelatinous material. The optic chiasma was displaced against the left internal carotid artery.

Histologically the tumour was found to be a typical adamantinoma.

Case 19.—*Male, aged 55. Married. Onset at 50. Loss of libido and of body hair. Amblyopia. Drowsy. Somnolent. Slight obesity. Feminine habitus. Genital atrophy. Absent body hair. Visual acuity markedly reduced. Optic atrophy. Bitemporal hemianopia. Sella enlarged. Cyst of infundibulum found on operation. Death. Autopsy : subpituitary cyst of Rathke's pouch.*

Case 19.—Charles T., a 55-year-old married man, was admitted to the service of Dr. Gordon Holmes on January 24, 1929. For the five preceding years there had been absence of libido, and he had observed a marked diminution in the frequency with which he needed to shave. For two years there had been loss of pubic hair. Six months before admission he suddenly noticed dimness of vision in his left eye. Soon after this there was loss of the temporal field and progressive deterioration of vision. During this time he had become somewhat drowsy and somnolent; but there was no history of further visual or metabolic disturbances.

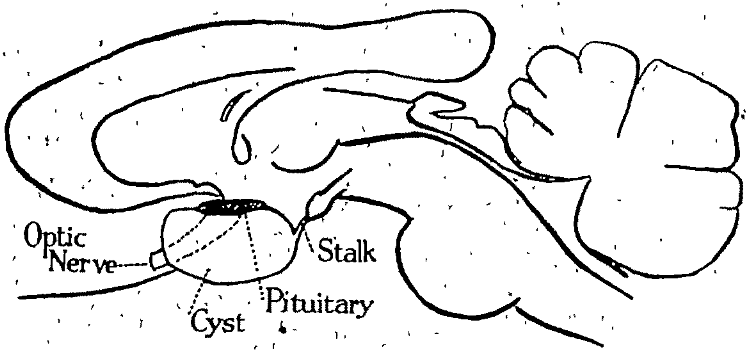


FIG. 1 (*Case* 19).—To show the relation of the cyst to the pituitary and chiasma.

The patient measured 5 ft. 10½ in. and weighed 182 lb. His pelvis was somewhat wider than his shoulders, and his arms and legs were thin and tapering. There was a pad of fat around his neck, an axillary band, a moderate panniculus, a small suprapubic fat-pad, and a tendency to a large pelvic girdle. His skin was soft and waxy. The hair was very fine, dry, and lustreless. The eyebrows were thinned out laterally. The moustache was sparse. There was no hair in the axillæ, or over the trunk or limbs. Pubic hair was exceedingly scanty and of a feminine distribution. The genitalia were very small.

Visual acuity on the right was $\frac{6}{18}$ and less than $\frac{1}{60}$ in the left. The fundi showed bilateral optic atrophy, more marked in the left. The right visual field had a temporal hemianopia, sparing the fixation point. The visual field of the left eye also showed a complete temporal loss, but including the fixation point and invading the nasal field from the temporal side.

The blood-pressure on successive examinations was 160/95 and 140/90.

Sugar tolerance: resting, 0·110; one and a half hours, 0·177; two and a half hours, 0·103.

X-ray showed irregular enlargement of the sella, with spreading of both anterior and posterior clinoid processes and absorption of the posterior clinoids. (Plate VIII, fig. 7.)

On February 15, 1929, Sir Percy Sargent made a right frontal approach. The dorsum sellæ was bulging and fluctuant. When punctured it was found to contain a brownish fluid. The right optic nerve lay over the bulge; the medial portion was pink, while the outer portion was pale.

The patient died the same day.

At autopsy a cyst was found, filling the sella turcica, which it had eroded on the left side. It lay below the optic nerve which was stretched out over it. Within the sella itself no trace of the pituitary body could be seen, but a yellowish softened mass of tissue lay on the upper surface of the cyst pressed against the floor of the brain. On histological examination this proved to be the normal pituitary gland displaced upwards by the cyst. Behind this yellowish mass the infundibulum entered the thickened wall of the cyst, giving it its only attachment to the brain, and presumably reached the pituitary body in the cyst wall. (Fig. 1.)

The posterior clinoid processes were thinned to membranous density and were embedded in the posterior wall of the cyst, which was also adherent to the dura mater of the tentorium.

Histologically, the cyst wall consisted only of fibrous, vascular and chronic inflammatory tissue. (Cf. Case 7.)

Case 20.—Male, aged 52. Married. Onset at 51. Amblyopia, headache, loss of hair, memory difficulty. Visual acuity markedly reduced. Discs normal. Bitemporal hemianopia. Enlarged sella. Tumour of the stalk found on operation. Recovery, with improvement. Histologically: resembling a medullo-epithelioma.

Case 20.—Arthur C., a 51-year-old married man, was admitted to the service of Dr. W. J. Adie on September 7, 1928. Five months earlier he had noticed a mist before his eyes. At the same time he began to suffer from headaches which occurred in both temples, in the centre of the forehead, and in the vertex; but which seemed to reach maximum intensity over the right eye. These headaches were accompanied by sharp shooting pains which would continue for some hours and then give way to duller pain. His free intervals rarely exceeded one day. The pain was aggravated by stooping and relieved by lying down. Three months later his right eye became quite blind, but after some weeks he noted some recovery of vision in the nasal field. At the same time he found that the temporal field of the left eye was blind. For one month before his admission he had observed a loss of hair from his arms and legs and some difficulty with his memory. No further endocrine or metabolic disturbances occurred.

The patient was a thin man, 5 ft. 8 in. tall and weighing 150 lb. There was general hypotrichosis and a waxy, pale, thin skin. With the right eye he could barely count fingers, and the visual field could not be outlined. Visual acuity of the left eye was $\frac{6}{36}$, and there was a complete loss of the temporal field for white and red, just sparing the fixation point. Both discs appeared quite normal.

X-ray showed an enlarged sella turcica with erosion of the posterior clinoids. (Plate VIII, fig. 8.)

On October 12, 1928, Sir Percy Sargent exposed the sella turcica. The optic nerve was seen stretched over the distended diaphragma sellæ. On opening the pituitary fossa a firm white tumour was seen. This was scooped out and aspirated.

Histologically, the tissue removed at operation consisted largely of cells arranged in columns and rosettes, a columnar epithelium suggesting a medullo-epithelioma, derived perhaps from an ependymal rest in the neural stalk of the gland.

After the operation the vision in the left eye improved to an acuity of $\frac{6}{18}$ without alteration of the field. The right eye was essentially unchanged. In November the patient was discharged, generally improved.

He was examined again in April, 1929, just six months after his operation. At this time his chief symptoms were: (1) Headaches high up in the right forehead which usually awakened him in the early morning and sometimes lasted throughout the day, but without nausea or vomiting; (2) anorexia; (3) a parched feeling in his throat which he could allay for an hour by swallowing one or two sips of water. (His output of urine was not increased); (4) Persistent dimness of vision. He said spontaneously that he felt as though he were looking through a high, narrow circle.

There had been no change in his weight, his hair distribution or his genitalia. Libido was absent, however. There was anosmia on the side of the operation. Visual acuity was $\frac{1}{60}$ in the right eye, and $\frac{6}{60}$ in the left. Both discs showed slight but definite pallor, chiefly on the temporal margins. Vision was present solely in the upper nasal quadrants of both visual fields. In the field of the right eye the seeing area did not extend to the mid-vertical line nor to the fixation point. There were no disturbances of the cranial nerves, reflexes or motor system.

Case 21.—*Male, aged* 60. *Married. Onset at* 55. *Gain in weight. Diminishing libido. Amblyopia. Obesity. Loss of body hair. Marked reduction in visual acuity. Unilateral optic atrophy. Bitemporal hemianopia. Cystic tumour of infundibulum found on operation. Contents aspirated. Temporary improvement. Second operation. Temporary improvement; gradual decline and death. No autopsy.*

Case 21.[1]—E. K. G., a 60-year-old married man, was seen in private by Dr. Gordon Holmes on February 16, 1925. For four or five years his weight had been increasing and his libido diminishing; but whether this was due to his tumour or to his age might be debated. Just eleven months before coming under observation he experienced difficulty in seeing clearly with the left eye. Within a few months acuity in the left eye was found to have fallen to $\frac{6}{60}$, without reduction in the right. The visual field of the right eye showed a gradual temporal loss, beginning in the upper quadrant. That of the left eye went through a short period of almost complete blindness, with preservation of only an island of vision in the upper nasal field; and then showed some spontaneous recovery, so that only a complete temporal loss persisted, the defect passing through the fixation point. There were no headaches at any time through the illness.

---

[1] Critchley and Ironside; Case 7.

On examination the patient proved to be somewhat obese, especially about the hips. His eyebrows were thinned, laterally. His moustache and beard were sparse. The upper margin of the pubic hair was transverse. The genitalia themselves were normal in size. Visual acuity in the right eye was $\frac{6}{18}$, and in the left eye $\frac{6}{60}$. The left disc was pale, but the right was of good colour. The right field showed a complete temporal loss with a defect in colour vision at the macular area. The visual field of the left eye also had a complete temporal loss, with a well-developed central scotoma.

On February 27, 1925, Sir Percy Sargent operated and found a large cyst of the infundibulum containing cholesterin. The cyst was incised and the contents aspirated.

One month after the operation the patient had recovered partial vision in the temporal field of the right eye and good central vision for colour; and in the left eye peripheral vision was good in all directions, but a large central area of relative scotoma persisted. Acuity in this eye had improved to $\frac{6}{18}$.

One month later, however, acuity had dropped to $\frac{6}{60}$ in both eyes, with the development again of a complete bitemporal loss and large central scotoma. The right disc still retained good colour, but the left disc was pale.

On May 2, 1925, the patient was again operated upon by Sir Percy Sargent. This time, in addition to evacuation of the contents of the cyst, a part of the wall was excised.

After a short initial improvement the patient became quite blind in the left eye and nearly blind in the right. Then he began to gain weight rapidly and became somnolent. From then on his course was steadily downhill, with a final period of weakness and delirium. He died January 6, 1926.

No autopsy was permitted. The tissues removed at operation proved to be typically adamantinomatous.

DISCUSSION ON THE CLINICAL FEATURES OF HYPOPHYSEAL STALK TUMOURS.

Intracranial Pressure.

It was reasonable to anticipate that large, cystic tumours of the hypophyseal stalk would give more interference with the circulation of the cerebrospinal fluid, and therefore a more constant tendency to the production of increased intracranial pressure, than either adenoma or the more solid and circumscribed suprasellar endothelioma. Critchley and Ironside [8], Holmes and Sargent [25], and Peet [33], have pointed out that because of this the presence of papillœdema may be of value in establishing a differential diagnosis between these three conditions. Unfortunately, however, the occurrence of increased intracranial pressure in early stages of the disease seems to be largely confined to those tumours of the hypophyseal stalk which manifest themselves in childhood or adolescence.

In Table II the occurrence of bouts of diffuse headache with vomiting, and the incidence of papillœdema, are given for this group of patients. Headaches with vomiting were found in seven out of the nine youngest patients. Papillœdema occurred in four of the first six cases. None of the remaining cases showed any evidences of increased intracranial pressure except Case 13, in which vomiting occurred as a late development, with an associated low-grade papillœdema.

In this respect all of the older cases of stalk tumour resembled the cases of adenoma and endothelioma. Vomiting in association with headache occurred in but two of the adenomata, and in no case of endothelioma. Papillœdema was found in none of the adenomata, and in only one case of endothelioma, in which it was apparently superimposed upon optic atrophy.

TABLE II.—INCREASED INTRACRANIAL PRESSURE: HYPOPHYSEAL STALK TUMOURS.

Case	Age onset	Bouts of diffuse headache with vomiting	Papillœdema
1	8	+	++
2	9	o	o
3	10	+	++
4	11	+	++
5	14	+	++
6	14	o ?	o
7	16	+	o
8	17	+	o
9	17	+	o
10	18	o	o
11	22	o	o
12	32	o	o
13	32	+ (late only)	+ (2D)
14	33	o	o
15	34	o	o
16	37	o	o
17	43	o	o
18	44	o	o
19	50	o	o
20	52	o	o
21	54-58	o	o

Without attempting to exhaust the literature, we have compared this table—in so far as it was possible—with a group of 23 reported cases, selected at random from: Bailey, 1924 [2] Cases 1, 2, 3; Cornil, 1925 [7] 1 case; Critchley and Ironside [8] Cases 5 and 6 (their other five cases are included in this report). Duffy [18] Cases 1, 2, 3, 4; Farnell [21] 1 case; Lanman and Smith [26] 1 case; Mackay and Bruce [27] 1 case; Olivecrona and Lysholm [30] Cases 1, 2; Babinski-Onanoff [1] [31] Case 1; Orzechowski and Mitkus [32] 1 case; Peet [33] Cases 1, 2, 3; Puusepp [34] Cases 1, 2; Strada [37] 1 case; Warthin [41] 1 case. In seven of this group of cases the onset of symptoms occurred after the age of 20; and of these seven only one showed definite early papillœdema with headache and vomiting (Olivecrona and Lysholm [30] Case 2, onset at 48). In Farnell's case, with the onset at 35, the disc was first found to be pink with slightly hazy edges, "possibly" representing "a beginning neuritis"; but it was not until the terminal stages of the disease, eight years later, that full-blown papillœdema occurred.

Headache.

Headache or local pain occurred in nineteen of the twenty-one cases of stalk tumour; in seventeen of the twenty adenomata; and in eight of the nine endotheliomata. The two cases of stalk tumour which were free from pain of any kind (Cases 19 and 21) were both in the sixth decade of life when their symptoms began (Table III).

The headaches and pain of which these patients complain are variable. The same patient may, at different stages of his illness or even within the course of a single day, complain of pains which are different not only in their character but in their location. In our experience this variability seems to be equally true of all three types of tumour. (Cf. Dott and Bailey [16].)

The headache may be diffuse and generalized, but this is found largely in the stalk tumours in children and adolescents, in whom increased intracranial pressure occurs. All of the others tend to have pain which is localized.

Pain in the forehead, above the eyes, in or behind the eyes, was described by eleven of the fifteen older patients with stalk tumours, by sixteen of the twenty adenomata, and by four of the nine endotheliomata. Transtemporal pain occurred in four of the twenty adenomata, in one endothelioma and in no stalk tumour. No other exclusive or predominant incidence is seen.

Pain is variously described as arising in one side or the other, in the forehead or the occiput, and as radiating thence either forwards or backwards, or into the vertex. Suboccipital pain and stiffness of the neck sometimes occur. The pain may be steady or paroxysmal, it may be dull, aching, or a mere feeling of pressure; or it may be excruciating in its intensity. Lancinating and stabbing pains sometimes are described, and occasionally burning sensations or skin tenderness over the painful area. Rarely, in association with the head pain, patients complain of stiffness, numbness, tingling, aching in the shoulders, down the spine, or in the limbs.

This experience corresponds with that described by de Schweinitz in his Bowman Lecture in 1923 [35].

Pain preceded the development of visual difficulties in six of the eight youngest cases of stalk tumour. But in nine of the eleven older cases the pain came on either simultaneously with, or after the onset of the visual disturbances. Of the sixteen cases of adenomata who had definite histories of pain, in thirteen the pain began either simultaneously with or after the onset of the eye disturbances. The same was found in five of the eight endotheliomata. Here again is seen the tendency of the manifestations of a hypophyseal stalk tumour to approach closer with advancing years to the clinical picture of the adenomata and the endotheliomata.

TABLE III.

	Stalk tumours			
	Cases 1—6	Cases 7—21	Adenomata	Endo-theliomata
Total number of Cases	6	15	20	9
Head pain or headache absent	—	2	3	1
Headache with vomiting	4	3	9	—
Headache without vomiting	2	9	15	8
Relation of Onset of Pain to Onset of Visual Disturbance.				
Pain occurring first	4	4	3	3
Both occurring together—or pain not occurring until after the visual disturbances	2	8	13	5
Site of Pain.				
Frontal and glabellar	—	6	9	—
Orbital, supra-orbital, or retro-orbital	—	6	9	4
Temporal (one-sided)	2	2	2	1
Transtemporal	—	—	4	1
Vertical	1	3	—	3
Occipital or suboccipital	4	5	2	1
Type of Pain.				
Continuous	2	1	1	—
Paroxysmal	4	4	3	2
With associated paræsthesiæ	—	2	3	1

Visual Disturbances.

(1) *Visual Fields.*—The defects in the visual fields to which intrasellar tumours may give rise have been carefully studied by Cushing

and Walker [13, 14], Traquair [38, 39], and de Schweinitz [35], among many others. There is substantial agreement that the most common lesion is a bitemporal hemianopia which begins in the upper temporal quadrant, progresses to the inferior temporal quadrant, and later involves the nasal fields. There is some disagreement as to whether the nasal fields are lost from above downwards or from below upwards. Among the cases presented here Case 9 showed a preservation of vision in both superior nasal fields alone; and Case 20, after operation, had similar fields. No case showed preservation of the inferior nasal fields without an intact superior field.

TABLE IV.—VISUAL DISTURBANCES.

	Stalk tumours		Adenomata	Endotheliomata
	Case 1—6	Case 7—21	20	9
Visual Fields.				
Normal	1	1	1	—
General constriction only	2	—	—	—
Bitemporal defects (based on histories and findings)	—	10	15	8
Lateral homonymous defects	2	1	—	—
Inferior homonymous defects	1	—	1	—
Uncertain field defects	1	3	3	1
Scotoma	—	4	1	2
Fundi.				
Normal	—	4	2 (unilateral) 2 (bilateral)	—
Pallor or optic atrophy	2	10	2 (unilateral) 16 (bilateral)	9
Papillœdema	4	1	—	1
Diplopia	5	4	6	1
Associated external ocular palsies	2	1	1	1

It is obvious from Table IV that the nature of the field defect is not of differential value. Bitemporal loss was quite as consistently found in the older group of stalk tumours as in the adenomata or endotheliomata. It was only among the cases in children that this was not the predominant defect, and here the youth of the patient and the difficulty of examination in the face of distress from increased intracranial pressure make it unsafe to draw any conclusions as to the exact nature of the loss.

Lateral homonymous defects were recorded in only three cases of stalk tumour, and in none of the others. In these three cases the growth was found at autopsy to extend posteriorly along the base in close relationship to the cerebral peduncles, where presumably it had not only involved the optic tracts, but had also interfered sufficiently with the circulation of the cerebrospinal fluid to produce increased intracranial pressure (with papillœdema in two of the cases).

Inferior homonymous defects, such as one might expect upon theoretical grounds in suprasellar tumours, were found only once in this series (Case 6). It occurred also in one adenoma of the pars anterior. Case 6 is of particular interest, because at operation the tumour was seen to be *lifting the optic chiasma from below.* Despite this fact the defect was predominantly in the inferior temporal quadrants. Such an observation as this makes it unsafe to conclude with Critchley and Ironside [8], and with Peet [33], that a stalk tumour which arises from the upper "anlage" will give rise to inferior field defects, whereas one which arises from the lower anlage will give rise to superior defects.

(2) *Diplopia.*—Diplopia occurred in nine of the twenty-one cases of stalk tumour; in one of them only after operation (Case 17). In six of the nine cases there were either definitely correlated extra-ocular palsies, or else the diplopia occurred as part of a general increase of intracranial pressure, and was presumably due to a fleeting sixth-nerve palsy. In the other three cases there was no trace or possibility of muscular weakness to account for the episodes of diplopia. Among the twenty cases of adenoma there were six in whom similar episodic diplopia occurred without any accompanying weakness of the extrinsic muscles of the eye. Diplopia was found once among the cases of endothelioma.

It is evident, therefore, that diplopia can arise in cases of stalk tumour in young patients as a result of increased intracranial pressure and extra-ocular palsies. But it is equally clear that diplopia occurs both among the stalk tumours and in adenoma of the pars anterior and in suprasellar endothelioma without any such explanation. In a forthcoming study an effort will be made to show that diplopia in these cases occurs only in the presence of heteronymous defects of the visual fields (chiefly bitemporal), with sudden episodes in which macular vision is sharply reduced. In such a period binocular vision becomes possible only with the use of heteronymous fields, and diplopia results.[1]

(3) *Fundi.*—The incidence of normal fundi seems to be about the same in the older group of stalk tumours as in the adenomata.

Table IV shows papillœdema to be the common finding among the younger patients with stalk tumour. Only one adult (Case 13) had any swelling of the discs, and in this case it amounted to only two dioptres. In no case was the papillœdema superimposed upon atrophy, but appeared rather as acute and high-grade swelling of 4-5 D, as part of the general increase of intracranial pressure which occurred in these young patients. No case of adenoma showed papillœdema. One endothelioma had two dioptres of swelling superimposed upon optic atrophy.

---

[1] L. S. Kubie and J. W. Beckmann. "Diplopia without Extra-ocular Palsies, caused by Heteronymous Defects in the Visual Fields associated with Defective Macular Vision," *Brain*, 1929. (In press.)

(4) *Symmetry.*—In Table V it is seen that in approximately half of the stalk tumours or adenomas the onset of the visual symptoms occurred simultaneously in both eyes, whereas this was true in only one of the nine cases of endothelioma. Similarly, in only two of the endotheliomas was the ultimate defect in visual acuity equal in both eyes, symmetrical reduction of acuity occurring on the other hand quite frequently in the other two groups. Among the stalk tumours it is also seen that where visual symptoms came on asynchronously, the time interval between their appearance in the two eyes was never as long as in the other two groups.

TABLE V.—SYMMETRY OF VISUAL DISTURBANCES.

	Stalk tumours	Adenomas	Endo-theliomas
Onset simultaneous in both eyes	9	6	1
Ultimate defect in visual acuity approximately equal in both eyes	12	8 (9 ?)	2
Onset occurring in one eye definitely before the other	11	11	7
Time intervals in months between appearance of symptoms in the two eyes (where known)	2, 3, 4, 6, 6, 8, 12, 18	2, 9, 9, 18, 24, 84, 108	2, 9, 36, 48, 48, 108
Ultimate defect in visual acuity unequal in the two eyes	7	11	7

THE ENDOCRINE DISTURBANCES.

(1) The first ten cases of our series (with their symptoms becoming manifest at the ages of 8, 9, 10, 11, 14, 14, 16, 17 and 18) have in common the fact that each of them showed a life-long defect in growth and development. Stunting was present in some degree in all. In certain cases (Cases 2, 3, 9 and 10) the history made it clear that obesity was later superimposed upon the failure of growth. In some of our records it is not possible to trace the order in which these manifestations occurred; but in Cases 6 and 7 it is probable that the obesity had been life-long; and in Case 7 there is the interesting suggestion that cessation of growth had occurred suddenly at the age of 16, two years

before coming under observation. Cases 1, 4, 5 and 8 apparently showed stunting without obesity. (Table VI.)

It is clear, therefore, that the picture which one may find depends upon the stage in which the patient is seen; since certain patients after showing stunting alone for years, afterwards developed obesity, whereas another was first obese and later ceased to grow, and still another was always both obese and under-developed.

Of the three boys, only two (Cases 3 and 6) were obese, and in both of these the body had a suggestively feminine configuration. In one the obesity was present from the start, but in the other it was a late development, which suggests that the Fröhlich syndrome may begin before puberty or may be superimposed upon a Lorrain type of dystrophy.

None of the six older cases of this group of ten children and adolescents had passed through a normal sexual pubescence. Of the females, only one had menstruated; and in this one patient (Case 9) amenorrhœa occurred at the age of 17 as an initial symptom of her illness.

Axillary and pubic hair was absent or scanty in each of these patients. This was presumably due to failure of hair growth in all but Case 9, where there was a definite story of loss of hair.

Late in the development of their symptoms, Cases 2, 8 and 10 had some disturbance of water balance, suggesting a mild diabetes insipidus.

(2) The next eleven cases of our series constitute a group in which the symptoms became manifest at the ages of 22, 32, 32, 32, 34, 37, 43, 44, 50, 52 and 54; in these no failure of growth was found. The majority of these cases presented a picture of obesity, amenorrhœa or loss of libido, and hair dystrophy.

Obesity was marked in eight cases, doubtful in Case 17, absent in Case 20, and in Case 13 the record was defective. Seven of these eight cases had amenorrhœa or loss of libido, and all of them had scanty or absent body hair. (Case 13 had amenorrhœa, with no observations as to body weight; Case 16 was obese, but the record lacked a menstrual history.) In six of the seven cases the onset of amenorrhœa or loss of libido was simultaneous with the appearance of obesity (Cases 11, 12, 14, 15, 18 and 19). In Case 21 obesity preceded loss of libido by twelve months.

It is striking that not a single woman patient in this series was married, suggesting an early disturbance in the psycho-sexual constitution; on the contrary, six of seven adult men were married.

Cases 11, 12, 14, 15 and 18 began to gain weight at the same time that visual difficulties or pain appeared. Cases 16, 19 and 21, however, began to grow obese three to five years before the onset of eye symptoms or pain. It is perhaps of interest that these three cases are in the group of six oldest patients, and that two of the three others had no obesity; so that in this final group of old patients obesity and endocrine disturbances in general occurred, if at all, long before the appearance of any other difficulties.

Thus there emerges from among the older patients a group in whom endocrine disturbances occurred long before the onset of any other symptoms, and another group in whom there was found little or no endrocrine disturbance of any kind. It is in this last group that the differentiation on purely clinical grounds from the suprasellar endotheliomata and from some of the adenomata of the pars anterior presents greatest difficulty.

The occurrence of these two groups of older patients is readily understood. At this age failing libido or amenorrhœa and a tendency towards obesity may be accepted with relatively little concern. It is only when headache and visual disturbances occur that such patients will seek medical advice. On the other hand, where headache and failing vision make themselves felt early, the patients will present themselves for immediate aid, before endocrine disturbances have occurred.

(3) *Water balance.*—In the entire series disturbances of water balance occurred in but six cases. With the exception of Case 2, all of these were found among the cases whose symptoms first appeared between the ages of 17 and 32. Of seven cases in this age-group there were two in which no disturbance of water balance is known to have occurred. In one of these, however, the record is defective.

In addition, Case 20 reported some months after operation that his mouth constantly felt dry and parched. This he could relieve, however, by taking a single swallow of water or milk, after which for half an hour he would be free from thirst. He had no polyuria. Atypical though this be, it is evidently a related type of disturbance.

In view of the present uncertainty as to the nature and mechanism of these disturbances of water balance (Bailey and Bremer [3], Fink [22], Snell and Rowntree [36]), it is not surprising that it was not possible to establish any correlation between the presence or absence of polydipsia and polyuria, and the size or position of the tumour mass or the structures pressed upon.

Polyphagia has been discounted in this review as of doubtful significance, as it was never seen alone. Snell and Rowntree [36] have pointed out that it may occur in diabetes insipidus as a result of the increased metabolic requirements of the patient which result from the heat debt incurred by the ingestion of large volumes of cold water.

(4) *Comparison with adenomata of the pars anterior.*—In fourteen of the twenty cases of adenoma of the pars anterior endocrine disturbances were found.

In general, however, the disturbance was less marked than in the stalk tumours. Obesity was present in seven of the twenty. Amenorrhœa or loss of libido was definite in four cases, and in three older women amenorrhœa occurred but might have been a menopausal change. Only one male of the five showed any tendency to a feminine type of fat distribution. Hair dystrophy was recorded but five times.

No stunting of growth occurred. Seven cases showed faintly suggestive evidences of transient acromegalic changes in the hands or facies (Bailey and Cushing [4]).

In only the youngest case was there any suggestion of a failure of sexual pubescence, and in keeping with this it is noteworthy that of the fourteen women eight were married, and of the six men five were married. In contrast to this, of the cases of stalk tumour not one of the eight women of marriageable age had married. The contrast does not hold true for the men, however, since most of the adult males in both groups had married.

Not one of the adenomas had suffered any disturbance of water balance.

(5) *Comparison with endothelioma.*—The endocrine disturbances among the endotheliomata were extremely slight. One male showed loss of libido and a mild diabetes insipidus. Two women had mild disturbances of water balance and symptoms which might have been menopausal rather than a result of their tumours. A third woman had amenorrhœa alone, which here again might have been menopausal.

Among the stalk tumours the only cases in whom endocrine disturbances are as slight as among the endotheliomata occur among the older patients (i.e. in the fifth and sixth decades).

In this respect the experience reported here is in essential agreement with that of Holmes and Sargent [25] and of Cushing and Eisenhardt [12].

(6) *Cachectic states.*—In Cases 2 and 5 of this series there were transient stages of emaciation and weakness during the course of the illness. These are the only examples of anything resembling the

so-called "pituitary cachexia" discussed by Frazier [23]. It would seem to be an open question whether these may justly be looked upon as essentially endocrine disturbances, or whether they may not be chronic manifestations of the same toxic factors which are more frequently observed as acute disturbances in tumours of the hypophyseal stalk.

TABLE VI.—ENDOCRINE DISTURBANCES.

	Stalk tumours		Adenomas	Endo-thelіomas
	Cases 1—10	Cases 11—21	(20)	(9)
Endocrine disturbance	10	8	14	8
Stunting of growth	10	—	—	—
Failure of sexual pubescence	9	—	1 ?	—
Obesity	6	8	7	—
Feminine habitus in a male	2	4	1	—
Hair dystrophy	10	8	5	—
Amenorrhœa or loss of libido	1	7	4 (3 ? menopause)	1 (3 ? menopause)
Disturbance of water balance	8	3	—	2 (1 ?)
Cachectic states	2	—	—	—

Blood-Sugar and Glucose Tolerance Studies.[1]

The accompanying table would indicate that no invariable criteria for differential diagnosis of these three types of tumour are furnished by studies either of the resting blood-sugar levels or of the response of the blood-sugar to the ingestion of the glucose.

TABLE VII.—GLUCOSE TOLERANCE CURVES.

(Based upon the ingestion of 50·0 grm. of glucose.)

	Stalk tumours		Adenomata	Endo-theliomata
	Cases 1—6	Cases 7—21		
Number of observations	1	8	13	7
Normal resting blood-sugar[1]	—	6	7	5
High resting blood-sugar	1	2	6	2
Normal curves[2]	—	1	—	3 (2 ?)
High rapid rise, normal fall	—	1	1	—
High rapid rise, slow fall	—	1	1	—
Rise to high level and delayed return	—	4	5	2
Normal rise with delayed fall	1	1	2	2
Slow rise to low level with slow fall	—	—	3	—

[1] 70 to 115 mgm./100 c.c.

[2] i.e., Curves which reach a maximum rise to about 180 in half an hour, and which fall to their own base-line or slightly below in one and a half hours.

The data tabulated here (Table VII) are somewhat at variance with the findings of Davidoff and Cushing [11, 15]. We have not encountered in these states of hypopituitarism the hypoglycæmia which they report, and the curve most frequently found in our material was a slow rise to a high level and a slow return, in place of the high tolerance which they emphasize. This is true both for the stalk tumours and the adenomas; but we are not in a position to say how many of these cases might have shown either faint clinical evidences of obsolete acromegaly, or also a scattering of chromaphil cells in the anterior lobe of the hypophysis (Bailey and Cushing [4]).

---

[1] These studies will shortly be presented in full by Dr. E. O'Flynn.

Somnolence, Apathy, Lassitude, &c.

Outspoken somnolence occurred at some stage of the illness, usually late, in nine of the stalk tumours, in two of the endotheliomata, and in one of the adenomata. Lassitude and fatigue, on the other hand, was not described by any of the patients with stalk tumours, but was found in one endothelioma, and in five of the twenty adenomas (Table VIII).

TABLE VIII.

	Stalk tumours		Adenomata	Endo-theliomata
	Cases 1—6	Cases 7—21	(20)	(9)
Somnolence	2 (4 ?)	6	1	2
Insomnia	1	1	2	—
Lassitude and fatigue	1	—	5	1
Depression	—	—	2	1
Attacks of unconsciousness	1	—	—	—
Sensorium defects (memory defects, &c.)	—	6	2	1

Somnolence among the stalk tumour cases became less frequent with advancing years—occurring in Cases 3, 5, 6, 7, 10, 11, 12, 13 and 19.

The only other mental disturbance which occurred with any consistency was a late state of slight intellectual reduction with mild difficulty in recent memory, slight confusion and dullness. This occurred in six cases of the stalk tumours (Cases 7, 9, 11, 12, 13 and 20), in one of the endotheliomata, and in two of the adenomata.

No correlation was demonstrable between the somnolence or other mental disturbances and the position or size of the growth and the structures pressed upon.

Toxic Reactions.

Among the twenty-one cases of hypophyseal stalk tumour toxic states occurred eight times. Five of these were in the six youngest cases (Cases 2, 3, 4, 5, 6), two among the young adults (Cases 10 and 11), and one in the older group (Case 16). In contrast to this no toxic states occurred among the endotheliomata. One case of adenoma had a definitely comparable episode; and two others had symptoms which might have been either toxic or menopausal.

The toxic reactions among the stalk tumours were of various kinds.

Case 2.—The illness began with an acute febrile state which had been diagnosed "meningitis," in which there were occipital headaches, uncertain visual difficulties, and transient unconsciousness.

Case 3.—An urticarial rash with hot flushes, lachrymation and cold hands, coincided with the onset of headaches, vomiting, and visual difficulties.

Case 4.—During the course of the development of the pressure symptoms this patient had an illness which was called "measles," but which was followed by marked and persistent listlessness.

Case 5.—Three months after the onset of pressure symptoms this patient had an episode of conjunctivitis.

Case 6.—One year before the onset of any other symptoms the patient had a skin eruption, which was called "herpes," on the right side of the face, associated with impaired hearing in the right ear.

Case 10.—At the age of 2½ the patient had an illness which was called "meningitis." The relation of this to her later illness and to her failure of normal development is problematical.

Case 11.—The patient's illness began with what was called "influenza of the head type." Immediately thereafter his headache and visual disturbances began.

Case 16.—Six years before her admission to the hospital this patient had an illness which was called "influenza"; and endocrine disturbances began immediately thereafter.

Of the adenomas, only one case is clearly comparable to these. This case had an acute illness, diagnosed as "influenza," which was characterized by frontal and temporal headache, vomiting, and peculiar head sensations. This was followed at once by the development of visual difficulties and endocrine disturbances. Another patient developed obesity and amenorrhœa at 44, hot flushes, shivering, a feeling of swelling in the extremities and tongue and short episodes of acute lumbar pain at 46, and in the following year developed headache and visual difficulties. A third case had amenorrhœa at the age of 47, and then complained of burning sensations in both arms at the age of 54 at the same time that visual disturbances began to appear.

The actual relationship of these "toxic states" to the development of the tumour is uncertain. Among the stalk tumours it may well be questioned whether certain of the instances quoted have any bearing.

The fact, however, that the rupture of a cyst may give rise to a sterile meningitis with pleocytosis and irritative and eruptive phenomena, as has been described by Worster-Drought and others [42], made it worth while to include every possible example.

Furthermore, in Cases 7, 17, and 21 of our series, following operation there were evidences of intense meningeal irritation, hyperthermia and urticaria, identical with the phenomena described by these writers and by Critchley and Ironside [8].

Symptoms from Pressure upon the Basal Ganglia, Brain-stem, Cerebellar Apparatus, and Olfactory Bulbs.

Orzechowski and Mitkus [32] and Van Bogaert [40] have described the occurrence of states of Parkinsonism and of thalamic dysthesiæ as a late manifestation of the upward growth and lateral pressure which tumours of the hypophyseal stalk may exert. In this series no example of Parkinsonism occurred, but several patients had pain which was referred to the extremities and along the spine and which might well have been of this nature.

Epileptic crises have been described by Dreyfus [17]. They were found in only one case of this series (Case 4), and in two endetheliomas, but no adenoma. In one of the endotheliomas the fits were initiated by unpleasant odours.

Tonic extensor spasms, resembling the phenomena of decerebrate rigidity, occurred in Case 4 of the stalk tumours a short time before death. In Case 2, as a terminal manifestation, there were flexor spasms which gradually became fairly fixed flexor postures. Occasionally extensor reflexes could be elicited by massive stimulation. In Case 13, before operation there was slight bilateral pyramidal involvement with extensor plantar responses. After operation bilateral spasticity and rigidity increased to a marked degree. Case 8 had bilateral patellar clonus, and Case 15 had bilateral extensor plantar responses.

Unilateral involvement of the cranial nerves or extremities was found in five of the stalk tumours.

Four of the cases of adenoma had unilateral extensor plantar responses without other motor or reflex disturbances. Among the endotheliomas one case showed a weakness of the third and sixth nerves on the right with a left hemiparesis, and another case had facial weakness on the right side, with possible weakness of the right arm.

It is seen that in this series signs and symptoms of pressure upon the brain-stem and basal ganglia are much more common among the cases of stalk tumour than in the other two groups.

Bailey [2] has reported the confusion that may occasionally rise between a suprasellar and a subtentorial neoplasm. In Cases 1 and 4 of this series subtentorial decompressions were performed. In both of these cases it was the youth of the patient and the marked increase in intracranial pressure which led to this procedure, rather than any marked cerebellar motor disturbances.

Disturbance of the sense of smell was found in one case of each of the three types of tumour. The loss was always unilateral.

X-ray Appearances.

In the accompanying sketches (Plates VII and VIII) are reproduced the sella outlines from all of the X-ray plates which we have been able to examine ourselves. They illustrate the varied changes which have been described by McKenzie and Sosman [28], Camp [5, 6] and Erdélyi [19], Dott and Bailey [16] and others. There is general agreement that the intrasellar adenoma usually causes a uniform ballooning of the floor of the sella into the sphenoidal sinus. The lower wall of the sinus and the floor of the sella remain parallel to each other unless there are anomalous spurs of bone crossing the sinus and giving irregular support to the sellar floor, or in children where the sinus is incompletely and irregularly formed (Camp [5]). According to Dott and Bailey [16], the clinoids may be partially absorbed; but with exposure of the plate adequate to record faint shadows, normal curves can usually be seen. This picture is given only rarely by tumours of the hypophyseal stalk; it occurs when they are entirely intrasellar and free from calcium. (Cf. Case 19, fig. 1, p. 149, and Plate VIII, fig. 7.)

More characteristic of the tumours of the hypophyseal stalk are the sella outlines seen in figs. 1, 2, 8 or 9. In the first the shape and size of the sella are quite normal, but both the anterior and posterior clinoid processes are almost wholly absorbed. In fig. 2 there is slight irregular enlargement of the cavity, especially posteriorly, with absorption of the posterior clinoids. In fig. 8 the sella is flattened out with marked increase in its antero-posterior dimensions. The floor is irregular. The anterior clinoids show marked rarefaction and short pointed spurs are all that remain of the posterior clinoids. Fig. 9 shows a sella that is flattened but small, with complete absorption of all the clinoid processes.

The X-ray picture which is most characteristic for tumours of the hypophyseal stalk, however, is that of intrasellar or suprasellar opacities

PLATE VII.

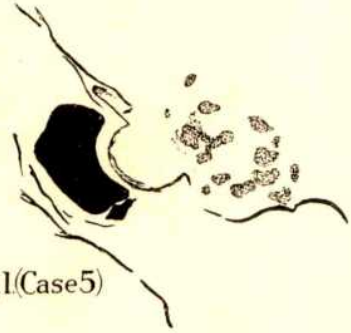


Fig1.(Case5)

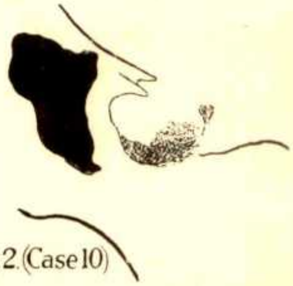


Fig.2.(Case10)

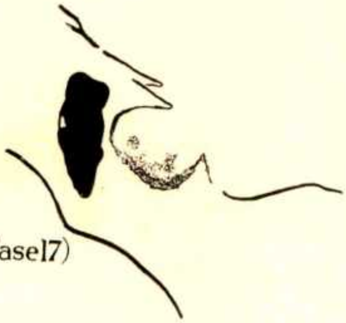


Fig3.(Case17)

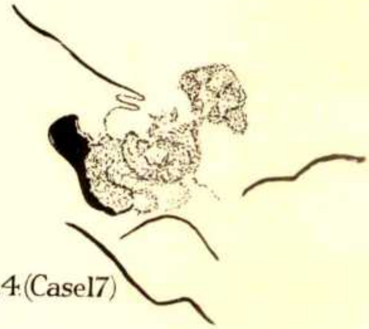


Fig.4.(Case17)

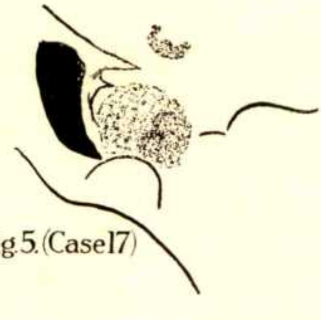


Fig.5.(Case17)

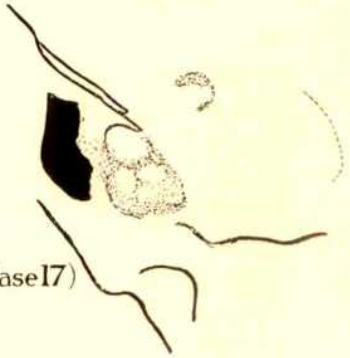


Fig6.(Case17)

To illustrate article by Dr. J. W. Beckmann and Dr. L. S. Kubie.

PLATE VIII.

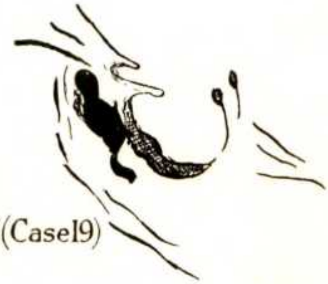


Fig 7. (Case 19)

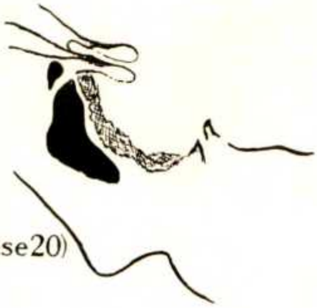


Fig. 8. (Case 20)

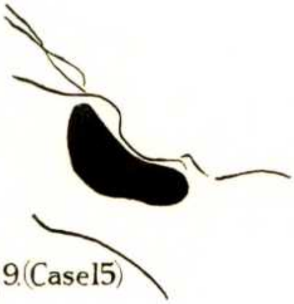


Fig. 9. (Case 15)

(figs. 1, 2, 3, 4, 5 and 6). These are reported to occur in from 70 to 80 per cent. of the cases (McKenzie and Sosman [28], Cushing [10]. Our data are too limited to offer any statistical generalization on this point.

That a suprasellar opacity is not peculiar to tumours of the hypophyseal stalk alone is shown by Case 5 of Heuer and Dandy [24], in which a similar shadow was seen in a case of tumour of the optic nerve sheath.

Figs. 3, 4, 5 and 6 are all from Case 17. Fig. 3 was made from the pictures that were taken before operation. Fig. 4 shows the condition two months after operation, fig. 5 three months and fig. 6 five months.

In fig. 6 an extensive suprasellar mass is indicated by the dotted line. In the stereoscopic plates this mass could be seen as a faintly calcified but very definite area

In contrast to the uniformity with which some deformation of the sella is found both in the hypophyseal stalk tumours and in the adenomata, in only one endothelioma of the group examined was there a suggestion of sellar enlargement. This coincides with the experiences of Holmes and Sargent [25] and of Cushing and Eisenhardt [12].

SUMMARY.

(1) Early evidence of increased intracranial pressure, such as diffuse headache with associated vomiting and papillœdema, occurs in tumours of the hypophyseal stalk only when the disease becomes manifest in childhood or adolescence. In older patients these indications of increased intracranial pressure occurred rarely, and only late in the course of the disease, and with less severity. Endotheliomata and adenomata rarely show signs of increased intracranial pressure, and then only as a late manifestation.

(2) Pain and headache are so variable in situation and character in all three types of tumour that they furnish no criteria for differential diagnosis.

Among the children and adolescents with stalk tumours, pain tended to precede the development of visual difficulties. But among the adults with this condition, as among the adenomata and endotheliomata, pain came on either simultaneously with or after the onset of visual disturbances.

(3) The nature of the visual field defect could not be satisfactorily studied in children. In adults with all three types of tumour the most

frequent defects were predominantly bitemporal. Lateral homonymous defects occurred in three stalk tumours and none of the others. Inferior homonymous defects occurred in one stalk tumour and one adenoma.

(4) Diplopia occurred on two bases: (*a*) as a result of extra-ocular motor palsies, chiefly in young patients with increased intracranial pressure; (*b*) as a result of heteronymous defects in the visual fields with a relative reduction of macular vision, forcing the use of heteronymous fields for binocular vision, with resulting diplopia.

(5) Endocrine disturbances were manifested in the ten younger patients by failure of growth and normal sexual development, i.e., stunting with or without obesity, failure of menstrual development, absence of body hair. Obesity occurred either early or as a late development. Where it occurred in males the body form became suggestively feminine.

Among the eleven older cases, eight showed endocrine disturbances of a regressive sexual nature, with obesity, loss of libido or amenorrhœa, hair dystrophy, &c. Despite the fact that no clear evidence of a developmental defect was present, no woman in this series was married. This was not true of the males.

Of the six oldest cases, three showed marked endocrine changes as the earliest manifestion of the tumour, and three showed little or no glandular disturbances of any kind. This group presents the most difficult problem in differential diagnosis.

Disturbances of water balance were found only six times in the twenty-one cases; all but one of these occurring in patients whose illnesses had begun between the ages of 17 and 32.

(6) In nine analyses no characteristic blood-sugar reactions could be made out.

(7) Outspoken somnolence occurred in but one of the adenomata and two endotheliomata, whereas it was found in nine cases of stalk tumour. Even here, however, its occurrence was late in the clinical history and practically confined to the children and young adults.

(8) Toxic states occurred in eight cases of stalk tumour, five of these among the six youngest patients, two in young adults, and one among the older patients. One adenoma had a comparable episode.

After operation three cases of stalk tumour had marked toxic reactions.

(9) Evidence of pressure upon the brain-stem and basal ganglia is seen more frequently in tumours of the hypophyseal stalk than in adenomata or endotheliomata.

(10) Sketches are presented illustrating the characteristic X-ray findings in tumours of the hypophyseal stalk.

It is a pleasure to acknowledge our debt to Dr. Gordon Holmes for his constant help and encouragement through the course of this study.

We wish to express our gratitude to the Medical Committee of the National Hospital, and to the several physicians under whose care these patients were, for their kindness in allowing us to report this material.

BIBLIOGRAPHY.

[1] Babinski, M. J. "Tumeurs de corps pituitaire sans acromégalie et avec arrêt de développement des organes génitaux," *Rev. Neurol.*, 1900, **8**, 531.

[2] Bailey, P. "Concerning the Cerebellar Symptoms produced by Suprasellar Tumours," *Arch. Neur. and Psych.*, 1924, **11**, 137.

[3] Bailey, P., and Bremer, F. "Experimental Diabetes Insipidus," *Arch. Int. Med.*, 1921, **28**, 773.

[4] Bailey, P., and Cushing, H. "Studies in Acromegaly. VII. The Microscopical Structure of the Adenomas in Acromegalic Dispituitarism (Fugitive Acromegaly)," *Amer. Journ. Pathol.*, 1928, **4**, 545.

[5] Camp, J. D. "The Normal and Pathological Anatomy of the Sella Turcica. II," *Amer. Journ. Roentgen.*, 1924, **12**, 143.

[6] *Idem.* "The Sella Turcica," *Journ. Amer. Med. Assoc.*, 1926, **86**, 164.

[7] Cornil, L. "Tumeurs du Tractus Pharyngo-hypophysaire," *Annales d'Anat.-pathol.*, 1926, **3**, 239.

[8] Critchley, M., and Ironside, R. N. "The Pituitary Adamantinomata," *Brain*, 1926, **49**, 437.

[9] Cushing, H. "Les syndromes hypophysaires au point de vue chirurgicale," *Rev. Neurol*, 1922, **29**, 779.

[10] *Idem.* "The Intracranial Tumours of Preadolescence," *Amer. Journ. Dis. of Children*, 1927, **33**, 551.

[11] Cushing, H., and Davidoff, L. M. "The Pathological Findings in Four Autopsied Cases of Acromegaly, &c.," Monographs of the Rockefeller Institute for Medical Research, 1927, No. 22.

[12] Cushing, H., and Eisenhardt, L. "Meningiomas arising from the Tuberculum Sellæ," *Arch. of Ophthalmol.*, 1929, N.S., **1**, 1 and 168.

[13] Cushing, H., and Walker, C. B. "Distortions of the Visual Field in Cases of Brain Tumour—Chiasmal Lesions with especial reference to Bitemporal Hemianopia," *Brain*, 1915, **37**, 341.

[14] *Idem.* "Chiasmal Lesions with especial reference to Homonymous Hemianopsia with Hypophyseal Tumours," *Arch. of Ophthalmol.*, 1918, **47**, 119.

[15] Davidoff, L. M., and Cushing, H. "Studies in Acromegaly. VI. The Disturbance in Carbohydrate Metabolism," *Arch. of Int. Med.*, 1927, **39**, 751.

[16] Dott, N. M., and Bailey, P. "Hypophyseal Adenomata," *Brit. Journ. of Surgery*, 1925, **13**, 314.

[17] Dreyfus, G. "Trois cas de tumeurs de la région hypophysaire avec crises épileptiques et symptômes adiposo-génitaux," *Rev. Neurol.*, 1925, **32** **ii**, 659.

[18] Duffy, W. C. "Hypophyseal Duct Tumours," *Annals of Surgery*, 1920, **72**, 537 and 725.

[19] Erdélyi, J. "Diagnostische Verwertung der mit Hypophysengeschwulsten zusammenhangenden Rontgenveranderungen," *Fortschritte Roentgenstrahlen*, 1928, **38**, ii, 280.

[20] Erdheim, J. "Ueber Hypophysenganggeschwülste und Hirncholesteatome," *Sitzungsb. d. K. Akad. d. Wissensch. Math. u. Natur. Klin.*, Abt. iii, Wien, 1904, **113**, 537.

[21] Farnell, F. J. "An Extracerebral Tumour in the Region of the Hypophysis," *N.Y. Med. Journ.*, 1911, **93**, 462.

[22] Fink, E. B. "Diabetes Insipidus, a Clinical Review and Analysis of Necropsy Reports," *Arch. of Pathol.*, 1928, **6**, 102.

[23] Frazier, C. H. "Pituitary Cachexia," *Arch. Neur. and Psych.*, 1929, **21**, 1.

[24] Heuer, G. J., and Dandy, W. E. "Roentgenography in the Localisation of Brain Tumours," *Johns Hopkins Hosp. Bull.*, 1916, **27**, 311.

[25] Holmes, G., and Sargent, P. "Suprasellar Endotheliomata," *Brain*, 1927, **50**, 518.

[26] Lanman, T. H., and Smith, L. W. "Hypophyseal Duct Tumour in a Child of Ten," *Surg. Gyn. and Obst.*, 1923, **36**, 361.

[27] Mackay, G., and Bruce, A. "Epithelioma of the Hypophyseal Duct," *Rev. of Neurol. and Psychiat.*, 1909, **7**, 445.

[28] McKenzie, K. G., and Sosman, M. C. "The Roentgenological Diagnosis of Craniopharyngeal Pouch Tumours," *Amer. Journ. Roentgen.*, 1924, **11**, 171.

[29] Martin, P., and Cushing, H. "Primary Gliomas of the Chiasm and Optic Nerves in their Intracranial Portion," *Arch. of Ophthalmol.*, 1923, **52**, 209.

[30] Olivecrona, H., and Lysholm, E. "Chirurgische Behandlung der Gehirntumoren," Berlin, 1927.

[31] Onanoff, J. "Sur un cas d'épithelioma," *Thèse de Paris*, 1892.

[32] Orzechowski, C., and Mitkus, W. "De la forme Parkinsonienne des tumeurs de la région infundibulo-hypophysaire," *Rev. Neurol.*, 1925, **32**, ii, 1.

[33] Peet, M. M. "Pituitary Adamantinomas," *Arch. of Surgery*, 1927, **15**. 829.

[34] Puussepp, L. "Die Tumoren des Gehirns, Ihre Symptomatologie, Diagnostik, und Operative Behandlung," Tartu-Dorpat, 1927.

[35] de Schweinitz, G. E. "Concerning Certain Ocular Aspects of Pituitary Body Disorders, mainly exclusive of the usual Central and Peripheral Hemianopic Field Defects," *Trans. of the Ophthalmol. Soc. of the United Kingdom*, 1923, **43**, 12.

[36] Snell, A. M., and Rowntree, L. G. "Clinical Manifestations of Water Intoxication in a Case of Severe Diabetes Insipidus. &c." *Endocrinology*, 1927, **11**, 209.

[37] Strada, F. "Beitrage zur Kenntniss der Geschwulste der Hypophyse und der Hypophysengegend," *Virchow's Archiv f. path. Anat.*, 1914, **203**, 1.

[38] Traquair, H. M. "Contribution to the Study of Bitemporal Hemianopia," *Edin. Med Journ.*, 1913, n.s. **11**, 197.

[39] *Idem.* "Bitemporal Hemianopia, Later Stages and Special Features of the Scotomata," *Brit. Journ. of Ophthalmol.*, 1917, **1**, 216, 281, 337.

[40] van Bogaert, L. "Thalamic and Parkinsonian Types of Infundibular Tumours," *Arch. Neurol. and Psych.*, 1928, **19**, 377.

[41] Warthin, E. A. "A Study of the Lipin Content of the Liver in Two Cases of Dyspituitarism," *Journ. Lab. and Clin. Med.*, 1916, **2**, 73.

[42] Worster-Drought, C., Carnegie-Dickson, W. E., and Crowhurst-Archer, D. W. "Dyspituitarism of the Lorain Type, associated with a Pituitary Cyst arising from Rathke's Cleft and Secondary Lesions in the Hypothalamic Region and Ventricles," *Brain*, 1927, **50**, 704.

THE PATHOLOGY OF MEASLES ENCEPHALOMYELITIS.

BY J. GODWIN GREENFIELD, B.Sc., M.D., F.R.C.P.

(*From the Laboratory, the National Hospital, Queen Square, W.C.1.*)

ENCEPHALITIS and myelitis have always been rare sequelæ of measles. But there can be no doubt that the frequency of such nervous complications has varied greatly from one period to another. One might almost speak of *epidemics of nervous sequelæ*, as during some years the cases have occurred in batches of six or more in certain populous districts, but the word *epidemic* is scarcely applicable to a condition which only attacks in any year one or two per million of the population. Such an increase of incidence has occurred on the Continent of Europe and in America during the past few years, and reached the London district in the spring of 1928. I had the opportunity of examining, within a period of three months, the cerebrospinal fluid in three cases and the brain in a fourth case, and I have hearsay evidence of the occurrence of other cases in the London area at about the same time. These cases presented a clinical picture which resembles closely, not only that of the European and American cases, but also that recorded many years ago in this country and on the Continent.

Historical.—The earliest case report in this country was given in 1790 by Mr. James Lucas, one of the surgeons to the General Infirmary at Leeds, under the heading of "An Account of Uncommon Symptoms following the Measles." It is remarkable that Sydenham in his description of the epidemics of the years 1670 and 1674 makes no mention of nervous sequelæ. Abercrombie in his book on "Diseases of the Brain and Spinal Cord" (1845 edition) records an interesting case in which paraplegia was followed some days later by signs of encephalitis. Henoch also records two fairly typical cases.

The fatal case recorded by Bergeron in 1868 is usually described as the first in which a pathological examination was made. But this case was not at all typical, and was much more probably one of diphtheritic paralysis. The weakness came on slowly and progressively some weeks after measles and was associated with nasal speech and difficulty in swallowing. A pathological examination of the cord by Ranvier revealed nothing beyond vascular congestion. The first satisfactory pathological description of a case of myelitis following measles was that given by Barlow and Penrose in 1886. In spite of the fact that several other cases occurred at about the same time as Barlow's, and that a further small outbreak of the disease occurred in the London district in 1904-05 (Batten, Smith, Pitt, Guthrie, Branson) no further satisfactory pathological examinations were recorded until the last few years. But about 1924 cases began to occur on the Continent of Europe and in America in increased numbers, and pathological reports were furnished by Bergenfeldt in 1924, by Winnicott and Gibbs, Brock and Mosse in 1926, and by Musser and Hauser and Wohlwill in 1928. Individual case reports from Germany, France and England between the years 1906 and 1924 indicated that the condition had not disappeared completely in this interval, but its rarity may be gauged from the opinions expressed in textbooks on infectious diseases published toward the end of this period. Thus Claude Ker in his book published in 1920 said that he had only seen one case of transverse myelitis and none of encephalitis in a series of 12,000 cases of measles, and that he was doubtful whether measles played any ætiological rôle in these conditions. Similarly Hegler, in Jochmann's textbook (1924), stated that he had only seen one case of myelitis following measles. In 1927, however, Neale and Appelbaum reported that they had seen eight cases in the State of New York in the year 1926 alone, and found that nervous sequelæ were much more common after measles than after any of the other infectious diseases. Similarly individual observers on the Continent whose clinical material was drawn from much smaller and less populous areas than New York State could report three or four cases seen within a few months of one another.

It is necessary to lay some stress on the periodicity of these visitations of the encephalomyelitis of measles because it will be found that other forms of encephalomyelitis, which present a very similar pathological picture, have had a similar periodical incidence. Thus diffuse encephalomyelitis or "neuroptico-myelitis," of which Devic gave a good description in 1894, and of which there were many case reports during the last twenty years of the nineteenth century, became much less common during the first twenty years of this century, to reappear again with greater frequency during the past few years. Similarly post-vaccinial encephalomyelitis which, as will be seen, resembles the encephalomyelitis of measles very closely, was unknown until the last decade, although a similar complication has been known for two centuries to follow smallpox (Freind, Clifton).

CLINICAL FORMS.

Although it may be rash to speak of a disease as a nosological ent when the few pathological examinations of cases which have been m have given somewhat divergent results, the similarity of the clin picture and the general agreement in the pathological descripti appear to justify this assumption. It is necessary for descrip purposes to separate the cerebral from the spinal form, although th are often combined; cases in which the most prominent symptoms spinal may give some evidence of cerebral involvement during the ea stages, or cases of severe convulsions and coma may be found to paraplegic after the acute cerebral symptoms have passed off. In b forms the disease tends to come on toward the end of the first we when the fever has subsided and when the rash is fading. The pati has often felt quite well again and may have been allowed out of bed

In the *cerebral form* there is then usually a recrudescence of fe with somnolence or delirium and often with convulsions. In alm every case the child is described as being soporose or even comat Some rigidity of the neck and limbs, a positive Kernig sign and *tá cérébrale* are almost constant and a moderate degree of head retractio often seen, so that meningitis may be suspected. Myoclonic moveme and jerkings of the limbs are common at this stage. There may definite paralysis of a hemiplegic or paraplegic type. Trism nystagmus and strabismus are not infrequently seen, and the face often described as being "mask-like." Papillœdema is fairly common temporary amaurosis has been observed in a number of cases, someti followed by loss of colour vision as the sight returns. In almost ev case there is incontinence of urine and fæces. In most cases somnolent state passes off after a few hours or a few days. The c then passes through a phase of irritability which may manifest itself choreiform movements, or by naughtiness and bad temper. The patie are described as "using all the bad words they know," or as "be remarkably rude for a child who was known to have been well brou up." This stage is fortunately of short duration in the majority of ca and, although in a few there may be some permanent change character, the majority recover completely in the course of a few d to a few weeks. Other, more focal, sequelæ may occur such as he plegia, aphasia or ataxia of a cerebellar type, but these may also co on suddenly without the characteristic period of stupor, as they may in the course of other fevers. Focal sequelæ are indeed remarka rare, when we consider the severity of the initial cerebral sympto

Epilepsy, most often of the *petit mal* type, may date from an attack of measles encephalitis.

It has been noted that the meningeal character of the symptoms has, in many cases, led to an erroneous diagnosis of meningitis. But the error may lie in the opposite direction, and several cases have been reported as measles encephalitis in which the correct diagnosis was probably that of local meningitis resulting from otitis media. The absence of any obvious focus of infection and the fact that the patient has felt quite well immediately before the onset of stupor, are points in favour of the diagnosis of encephalitis. On the other hand, when otitis media or infection of the nasal air sinuses is present by far the most likely diagnosis is that of meningitis.

The *spinal type* of the disease similarly may be ushered in by a recrudescence of fever, but this is not always present. The paralysis is usually confined to the lower half of the body and is almost always associated with loss of sphincter control. This is remarkably constant in the histories of reported cases, and it is noteworthy that it usually remains as long as the paraplegia. Lucas' case may be quoted as a typical example of this kind. An unmarried woman, aged 23, became feverish on June 21, and on the 23rd developed a measles rash. On the 28th the rash was fading and she felt well. On the evening of the 29th, however, " she perceived that she was deprived of the use of her lower limbs, although she had not any other uncommon complaint. The following morning she could not pass urine, and an obstinate constipation succeeded which was scarcely to be overcome by the most powerful cathartics administered not only by the mouth but also by clysters. She had little pain ; her chief complaint was a sense of fulness in the abdomen. The warm bath which was directed as a stimulus to the viscera was followed by a slight pain in the legs. During ten days no urine was evacuated except what escaped upon moving her, or was drawn off by the catheter which was daily employed. She neither passed urine at the time of the fæcal discharge, nor had any voluntary inclination to void it until her limbs had so far recovered that she was able to move over the floor. . . . . The patient was a week before she could move a limb, and yet in two days more she was able to walk over the floor without much aid." It is interesting to note that this patient had had a similar affection some years before following an attack of small-pox.

In Barlow's patient retention of urine was the first symptom, coming on with a rise of temperature three days after the rash. The next day he was drowsy and could not move his legs, but could feel in them. The following day he developed weakness of the arms and paralysis of the intercostal muscles and died on the same evening. Box's case is of interest from the presence of dissociated sensory loss. His patient, a girl of 14, became feverish on April 20, 1920, and had a well-developed measles rash on the 24th. On the 27th the legs were weak and there was difficulty in micturition. For this condition a hot-water bottle was applied to the abdomen and caused a burn, the pain of which was not felt until May 5, when power was returning to the legs. There was complete loss of sensibility to pain, heat and cold up to the sixth thoracic segment, with no loss whatever to light touch. She passed urine naturally for the first time on May 6, but did not regain control of the bowels until May 29.

The paralysis, which is usually at first flaccid, tends to become spastic after the first few days, with increase of the deep reflexes and the extensor type of plantar response. Here, too, the recovery is usually remarkably complete, there is little or no wasting, and the only abnormality found after a few weeks, as in Box's case, may be exaggeration of the deep reflexes, a doubtful Babinski sign and a tendency to precipitate micturition, or incomplete emptying of the bladder.

This picture of temporary paraplegia with loss of sphincter control and incomplete or dissociated anæsthesia is so characteristic of the myelitis following measles, that the few cases in which the paralysis has been of another type may be discounted. In some, as in that of Bergeron, the condition resembles post-diphtheritic paralysis so closely that we must consider the possibility of coincident infection with the Klebs-Loeffler bacillus. In others there is little doubt that the paralysis was due to an attack of poliomyelitis or Landry's paralysis following measles. The condition differed in no way from that usual in these diseases. The typical measles myelitis, on the other hand, resembles no other form of myelitis except that sometimes seen in the early stages of disseminated sclerosis and the myelitis which sometimes comes on during a course of antirabic treatment or during convalescence from some of the other acute fevers.

CLINICAL CASES.

For the notes of the following case I am indebted to Dr. C. P. Symonds.

Case 1.—W. F., a girl, aged 9, was seen in consultation with Dr. R. B. P. Lansdown at Purley on March 15, 1928. She had previously been healthy in every respect. Her brother had had measles three weeks before. A week before being seen she had developed a temperature, and two days later a typical measles rash. Two days after this her temperature was normal, and she seemed quite fit. The temperature then went up again, and she became listless and apathetic. She had no headache, there was no vomiting and no pain. On March 14 she was found to be stiff, with slight head retraction and Kernig's sign, and the suggested diagnosis was meningitis. On the day of examination she has been taking her food fairly well, with some difficulty in opening her mouth. She had not spoken, and her mother thought that she did not recognize people round her.

On examination she was awake and alive to her surroundings, but reacted slowly, as if she were at a distance. Occasionally she would say "Yes" or "No" in a whisper, with difficulty in opening her mouth. The optic discs were both congested, but there was no swelling. The pupils were equal, central, regular, and reacted to light. The ocular movements were very slow. There was imperfect co-operation but apparently full movement. There was no nystagmus. The corneal reflexes were present and equal. The face was expressionless, and there were clonic winking movements continuously at a slow rate. The lower facial muscles appeared to be in tonic spasm, as also the jaw muscles. The mouth could be passively opened only with great difficulty against this resistance. She had difficulty in opening her mouth to take fluids. She could not protrude her tongue on request. There appeared to be no sensory loss over the face.

There was no true head retraction, but she was in a condition of mild tonic spasm with retraction of the head; the arms were slightly abducted at the shoulders, semi-flexed at the elbows, strongly pronated and flexed at the wrists with the fingers hyper-extended. She could make some voluntary movements, as, for instance, taking hold of one's hand. The limbs could be placed in other postures and would remain there. The rigidity seemed of the clasp-knife type. The trunk was slightly extended, the lower limbs strongly extended with down-pointing feet and toes. No defect to pinprick was discovered. All tendon reflexes were brisk, and there was a brisk jaw-jerk. The abdominals were not obtained. The plantars were extensor. She was incontinent of urine.

She was rather under weight, but there were no physical signs of disease elsewhere in the body. The impression she gave was of an acute cerebral diplegia, probably due to "true measles encephalitis." A lumbar puncture was done, and clear fluid, not apparently under increased pressure, was obtained. This I examined with the following result. The fluid was clear and colourless without any coagulum. It contained fifteen mononuclear cells per cubic millimetre of which 12 per cent. were large mononuclears. No polymorphonuclear cells were present, and no tubercle bacilli or other organisms were seen in films of the centrifugalized deposit. The Nonne-Apelt and Pandy reactions were weakly positive. Chemical examination gave 40 mgm. protein. 800 mgm. chlorides and 79 mgm. glucose per 100 c.c. of fluid.

She died on March 16, but no post-mortem examination was allowed.

For the clinical notes of the two following cases I am indebted to Dr. Gordon Holmes.

Case 2.—A girl, aged 6, who had a dry ichthyotic skin, but had previously enjoyed good health, developed measles of moderate severity in the last week of March, 1928. The rash, which appeared on March 27, was abundant and severe, but not otherwise abnormal. The illness took a natural course till March 31, when, as the rash was beginning to fade, the child became drowsy and restless, and in the early afternoon had a severe general convulsion preceded by a cry. She recovered slowly from this convulsion, but before regaining consciousness had a few similar seizures. At irregular intervals during the afternoon and evening several other attacks occurred in which the right side of her face and her right limbs were involved in clonic spasms. In all of these the eyes deviated to the right and upwards; the clonic movements commenced in the face and occasionally were limited to it. In the majority the right hand and arm were involved in similar clonic spasms, but in the slighter seizures the right leg was in tonic extension. The left limbs were not involved. The pupils were contracted, the child became cyanosed, and her respirations were irregular and stertorous.

During the evening the attacks increased in severity despite the administration of bromide and luminal; they could be checked only by the inhalation of chloroform. Towards midnight the convulsions subsided gradually. The child then passed into a semi-stuporose state, her respirations were irregular and often of the Cheyne Stokes type, her eyes rolled about restlessly, but she did not move her limbs.

On the morning of April 1 she was conscious but took little interest in her surroundings, though she looked towards people who entered her room. Her right arm was flaccid and was never moved, and her right leg was very weak. She seemed to move her left limbs normally. The right side of her face was flattened and she did not speak, even in reply to questions, but occasionally uttered a short frightened cry. Her pupils were dilated, the left slightly larger than the right, and both reacted to light. Her fundi were normal. She swallowed slowly without difficulty, but during the day she was incontinent. Her arm-jerks, knee-jerks and ankle-jerks were slightly exaggerated, especially those of the right side, and both plantar reflexes were of the extensor type. There was no retraction of the head, Kernig's sign or other evidence of meningitis.

During the afternoon she became drowsy and occasionally slept for short periods. As the evening advanced her respirations became more rapid and irregular, her temperature rose and she became cyanosed. At 11 p.m. she started to have attacks, which were described as "general rigors" and which continued till she died at 1.30 a.m. on April 2. In these so-called "rigors" her whole body was involved in rapid clonic movements, except the right arm which became rigid with the fingers contracted. She was deeply unconscious and became very cyanosed.

An autopsy was performed on the following afternoon at 4.30 p.m., fifteen hours after death, by Dr. Holmes and myself.

Case 3.—A boy, aged 7½, developed measles, the rash appearing on April 10, 1928. The course of the illness was quite normal and not unusually severe;

his temperature did not rise above 103° F. On April 14, the rash was fading and the patient seemed to be passing into a normal convalescence; during the early hours of this afternoon, while alone, he fell from his bed to the floor and was found in the last phase of a general epileptiform convulsion, in which he bit his tongue and passed urine. He had four or five similar general convulsions during the evening and then passed from a semi-comatose state into a deep sleep in which abrupt jerky movements of his hands and trunk occurred.

In the early hours of the following morning the epileptiform seizures recurred every half to one hour, and in the intervals between them there were coarse clonic movements of his limbs, face and trunk, irregular in distribution and sharp or almost myoclonic in type. Towards midday the convulsions ceased, but the clonic movements became more frequent and more extensive, at times giving the impression that the boy was having severe rigors. Consciousness returned and the child frequently gave a short shrill cry of a "meningeal type," but he paid no attention to his surroundings and remained incontinent of urine.

When seen in the early afternoon he was in a stuporose state but frequently cried out when handled or disturbed in any way. His pulse was very rapid and his temperature 103·4° F. He was sweating profusely and was of a dusky almost cyanotic colour. His head was slightly retracted and an attempt to flex it on his chest produced evidences of pain. Kernig's sign was present in mild degree on both sides. His fundi oculi were normal; the ocular movements were apparently not restricted and there was no squint, while the pupils were moderate in size and reacted to light. His knee-jerks and other tendon reflexes were brisk, but the abdominal reflexes were not obtained, probably owing to rigidity of the abdominal walls. The plantar responses were extensor in type.

While under observation there were almost constant abrupt clonic movements of his limbs, which at times extended to his face and the muscles of his trunk. They affected irregularly now one limb or part of a limb, now another, but were occasionally so widely generalized, and so small in excursion, that they resembled the clonic spasms of a mild epileptic convulsion. Occasionally the jerks were so small in range and occurred in such rapid sequence that they suggested a severe rigor. Owing to the stuporous state it was impossible to test the strength or power of movement of his limbs, but there was no evidence of any severe degree of paresis. A lumbar puncture was done; the cerebrospinal fluid was under slightly increased pressure and my examination of it showed a clear, colourless fluid without coagulum. It contained 31 mononuclear cells per cubic millimetre of which 15 per cent. were of medium to large size. The Nonne-Apelt reaction was negative and the Pandy reaction weakly positive. There were 55 mgm. protein, 740 mgm. chlorides and 123 mgm. glucose per 100 c.c. of fluid.

During the evening of April 15 the child had another series of epileptic convulsions and died the next morning.

Permission to make an autopsy was refused.

I am indebted to Dr. James Collier for the following notes of a case of myelitis following measles in which I examined the cerebrospinal fluid.

Case 4.—(Dr. Collier's notes.)

Miss M. H., aged 24, was seen by me in consultation with Dr. Gardner, of Amersham, on June 8, 1928.

Fourteen days before she had contracted measles; there was an epidemic of measles in Amersham at the time. The illness was typical and the rash was profuse. The pyrexia lasted seven days. On the eighth day she complained of inability to pass urine and a catheter was used but there was no incontinence. During the following twenty-four hours she gradually lost all feeling in the legs as high as the hips and became completely paralysed in the legs. No voluntary micturition or action of the bowel was possible. There had been no pain. I saw her on the fourteenth day. She looked well and had no discomfort. The mottling typical of a waning measles rash was very obvious. There was complete flaccid palsy in effect below the iliac crests and the umbilicus shifted markedly upwards on raising the head from the pillow. The upper abdominal reflexes were brisk but those below the umbilicus were absent. Though she could make no movements of the lower limbs except feeble movements of all the toes, I made out with absolute certainty that she could put every muscle in both lower limbs into voluntary contraction. I could make out no loss of sensibility to pain, temperature or touch, but there was obvious diminution of vibration sense in the feet and toes. The legs were hypotonic and knee and ankle jerks were not obtained. The plantar reflexes were of flexor type. A lumbar puncture was performed and the cerebro-spinal fluid was examined by Dr. Greenfield who gave the following report: "The fluid is clear and colourless. It contains 6·5 cells per c.mm., and 50 mgm. of protein per 100 c.c. The globulin tests are weakly positive and Lange's gold sol reaction negative."

A highly favourable prognosis was made.

I saw her a week later. She was greatly improved. Power in the legs had returned to the extent that she was able to stand and walk feebly when supported between myself and Dr. Gardner. The lower abdominal reflexes had returned and knee and ankle jerks were obtained. The plantars were still of the flexor type. All muscles of the lower extremities and abdominal walls reacted well to faradism. There had been no incontinence but there had been no voluntary action of either bladder or bowel. I made a rectal examination and found the sphincter ani gripping well and she said that she was quite conscious of the presence of the finger within the anus.

She progressed well for several weeks but regained no sphincter control, In early July she was severely upset by the removal of a nurse that she liked and thereafter rapidly lost the power of walking. Dr. Gardner had been ill and away for two months and I did not see her between June 15 and early September. On the latter date I saw her again and found a purely functional paralysis and a purely naughty resolve not to pass her water without the catheter. She was then treated in a nursing home for a week by Dr. Carmichael and myself with marked improvement, but she was removed from our care thereafter.

She walked into Dr. Feiling's consulting room a few weeks later and had recovered from the sphincter trouble.

Pathological Examination of Case 2.

At the post-mortem examination the brain with the upper part of the cervical cord was removed, and through a small incision over the xiphisternum and epigastrium the general appearance of the heart and lungs and the upper abdominal viscera was made out. There was no evidence of pericarditis or pleurisy but the lower lobe of the left lung was somewhat collapsed, solid and airless, and on microscopic examination proved to be in a condition of collapse with early bronchopneumonia. The peritoneum was smooth and glistening. The spleen was slightly enlarged but firm, and microscopic section demonstrated in it a general excess of nuclei without much enlargement of the Malpighian bodies.

The intracranial venous sinuses were carefully examined for evidence of ante-mortem thrombosis but none was found. The brain was fixed *in toto* in 10 per cent. formol saline solution, and after a week in this fluid was cut into horizontal slabs 1 cm. thick. At this time the white matter of the centrum ovalé, which was not completely fixed, appeared diffusely pink as if stained with eosin. On this pink surface the cut vessels stood out strikingly as if distended with blood and a reddish halo was seen round many of them. In contrast to the intense congestion of the white matter the grey substance of the cortex and basal ganglia was not abnormally red. No hæmorrhages either of petechial or larger size could be made out.

Pieces 5 mm. thick of various parts of the cerebral and cerebellar hemispheres were taken for further investigation. These included the whole of the brain-stem from the middle of the medulla to a plane 2 cm. above the lowest level of the basal ganglia. Several pieces from the upper parts of the basal ganglia, the cortex, the dentate nucleus and cerebellar cortex and the second cervical segment were also examined.

The following methods were used. With frozen sections: Herxheimer's Scharlach R. with hæmalum, Bielschowsky's neurofibril method (Da Fano's modification), Cajal's gold-sublimate method for neuroglia, and Cone and Penfield's modification of Hortega's microglia stain. With celloidin embedding, toluidin blue staining for Nissl bodies, iron hæmatoxylin with eosin and with van Gieson's counterstain, Loyez' method for myelin sheaths, and Mallory's acid fuchsin—anilin blue—orange G stain. Some pieces were also examined by similar methods with paraffin embedding after re-fixation in Bouin's fluid.

The histological examination revealed three types of abnormality which were sometimes combined but sometimes found separately. These were: (1) intense and diffuse congestion of vessels with a few small hæmorrhages; (2) perivascular cuffing with mononuclear cells; (3) zones of early demyelination centred on a small vessel and spreading out a short distance into the tissues.

(1) The *congestion* was most evident in the white matter of the cerebral hemispheres, but was also present in the basal ganglia, mid-brain and pons, and to a less degree in the capillaries of the cortex. A small amount of hæmorrhage was present immediately around a few small venules, where it was confined to the perivascular space of His. It appeared that exudation of blood at low-pressure had ruptured the attachment of the neuroglial fibres to the periadventitial fibrous tissue sheath, and had pushed back the nervous tissue round a part of the vessel. In contrast to the usual picture in encephalitis lethargica the vessels from which such hæmorrhages had taken place were not necessarily those surrounded by cuffs of mononuclear cells. These hæmorrhages were of minute size and so few were seen that they would scarcely be considered worthy of mention were it not for the fact that hæmorrhages of this nature have formed a prominent part in the pathological picture of other cases.

(2) *Cuffs of mononuclear cells* were found round almost all the small veins of the centrum ovale, and also round some of those in the basal ganglia, midbrain, pons and medulla. A similar change, though of slighter degree, affected also a few of the cortical veins. These cuffs were rarely more than one cell and never more than two cells thick. All the affected vessels appeared to be veins, of which all sizes were affected. The arteries were quite free from cellular infiltration. The cells composing this exudate were of the lymphocytic class, and included numerous lymphoblasts and, round some vessels at any rate, a considerable number of plasma cells. The latter were found not only actually within the confines of the Virchow-Robin space but in the tissues immediately outside this. In no case were they present alone, nor were they even the most numerous cell type round any vessel. These cells were often flattened out either by the contraction of the outer wall of the Virchow-Robin space during fixation, or by the distension of the vessel with blood. The ring round many of the vessels was not complete, a small interval being present between the individual cells forming it. (Figs. 1 and 2.)

In addition to cells of the lymphocyte class, there were round a few vessels collections of fat granule cells, either forming the only contents of the Virchow-Robin space or intermingled with lymphocytes and plasma cells. These were naturally most obvious in sections stained by Scharlach R., but could be seen also by other cell stains. The vessels surrounded by a complete zone of fat granule cells were mostly small subcortical venules. The lipoid in the cells was in every case brilliantly anisotropic, or at least contained numerous anisotropic granules, and therefore was neither lipochrome, nor fully formed fat. That it was derived from myelin was confirmed by the presence in some of the larger granules of well defined "myelin crosses," when viewed under crossed Nicol prisms. Numerous colourless crystals of cholesterin were also present. Most of the vessels in the deeper parts of the white matter contained no fat granule cells, but in the wall of some fairly large vessels an occasional cell of this kind was seen. A few cells with reniform nucleus, apparently of endothelial origin, were also seen in this situation, but it was not quite clear whether they were free in the Virchow-Robin space or merely swollen endothelial cells attached to its walls.

(3) The *zones of perivascular demyelination* were by far the most characteristic abnormality seen in sections of the brain. They distinguished the pathological picture clearly from that of encephalitis lethargica and allied it to that of post-vaccinial encephalitis. They were, in fact, almost identical with the lesions found in very early cases of the latter disease. They were scattered throughout the brain and brain-stem, but were most numerous and of greatest width round the medium-sized vessels in the deeper parts of the centrum ovale. In sections stained with hæmatoxylin and eosin or van Gieson's counterstain they appeared as rather cellular zones surrounding some of the veins in a concentric manner. Examination with a higher power showed that in addition to the excess of nuclei in these areas the ground substance had lost its fibrillar structure and appeared homogeneous. With Scharlach R. no fatty granules could be demonstrated outside the perivascular sheath, but the affected zones did not take the terra-cotta staining of myelin, and thus looked paler than the rest of the tissue. The Weigert-Pal and Loyez methods demonstrated these zones of demyelination very effectively, and showed that they merged gradually into normally myelinated tissues, through a zone in which many of the myelin sheaths were thin or beaded. The great majority of the demyelinated zones were very narrow, but round some of the larger veins rather wider zones were found. None however was large enough to be visible to the naked eye.

The cells in these zones were of quite different type from those in the Virchow-Robin spaces. They were chiefly of two forms: (*a*) cells with polymorphic, darkly-staining nuclei and a cell body which either was quite without definition or was fairly large and granular with an irregularly rounded margin, (*b*) cells of the fibre-forming neuroglial type with oval nuclei. (Figs. 3 and 4)

In the cells belonging to class (*a*) the nucleus was of very varied form. In those without obvious cytoplasm it was reniform, rod-shaped, comma-like or triradiate, and some very bizarre forms were seen in which the nucleus was long, thinned out toward one end and irregularly bent. These cells were presumed to be of microglial origin and sections stained by Cone and Penfield's modification of Hortega's stain revealed long irregular processes stretching from elongated nuclei of this type, especially towards the outer part of the zones. The cells with a more defined cell body had for the most part lobed or reniform but compact nuclei. Elongated nuclei were not seen in cells of this type. By the Hortega method employed the cell body was clearly outlined as a loose-meshed sac, pear-shaped or irregularly oval in the more peripherally placed cells and more rounded in those nearest to the vessel wall (fig. 5). The appearances corresponded exactly to Hortega's drawings of microglial cells two days after an injury to the brain. This stain revealed changes in the microglia altogether outside the obvious zones of demyelination. Immediately round the zone of cell increase there was a zone, at least as wide or rather

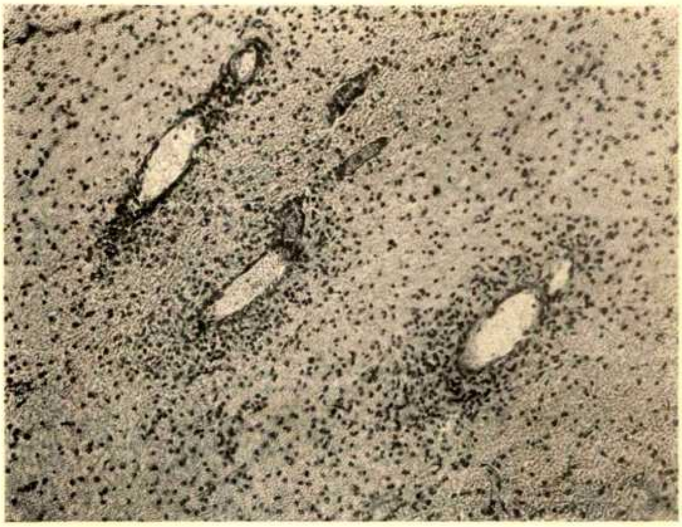


FIG. 1.—Three small vessels in subcortical white matter. Around each there is a more or less complete ring of mononuclear cells, and spreading out into the tissues are zones of "cellular proliferation," associated with demyelination. (Hæmatoxylin and van Gieson.)

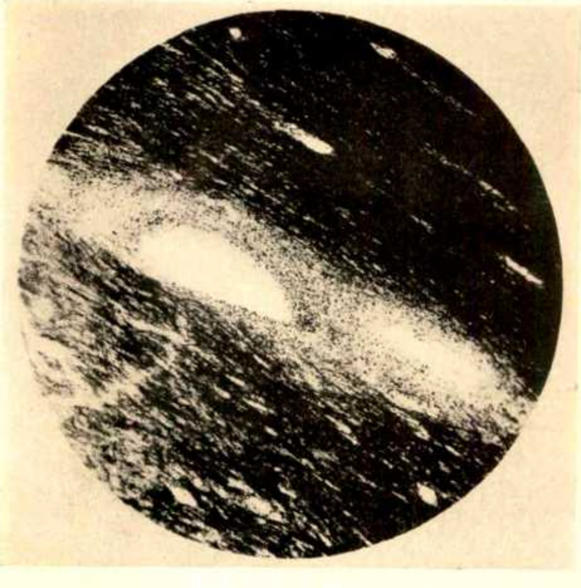


FIG. 2.—A similar vessel, as seen in a section stained for myelin sheaths, showing complete destruction of the myelin in the cellular zone round the vessel. (Loyez' hæmatoxylin.)

To illustrate article by Dr. J. Godwin Greenfield.

PLATE X.

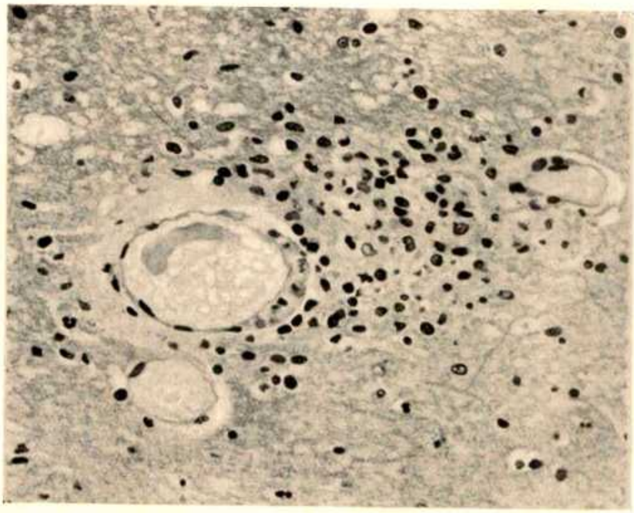


FIG. 3.—A higher power photograph of a perivascular zone of softening. Some fatty cells are seen in the Virchow Robin space. Outside this the cells have nuclei of very varied shape. (Hæmatoxylin and van Gieson.)

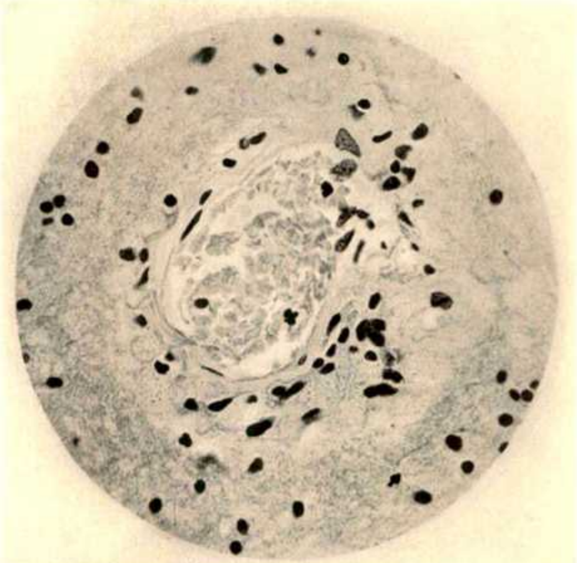


FIG. 4.—Photograph of a vessel surrounded by a slighter degree of perivascular demyelination. The area of pallor round the vessel indicates the zone of myelin destruction. (Hæmatoxylin and van Gieson.)

wider, in which the processes of the microglial cells were irregularly swollen, often with balloon-shaped swellings on them. This was the only obvious change in this zone, and by all other staining methods, except perhaps the Weigert-Pal method to which reference has been made, the tissue in this outer zone appeared normal.

(*b*) It is difficult to say whether the number of fibre-forming glial cells in perivascular zones was greater than normal. Certainly they were much less numerous than the cells of type (*a*) and no evidence of nuclear division could be seen in them. Nor was there any evidence of the formation of new fibres. In the majority, however, the cell body was somewhat swollen and more obvious than normal. In addition there were scattered through the perivascular zones individual cells with a multilobed nucleus and a small rounded cell body. These cells, which appeared to be polymorphonuclear leucocytes, were nowhere numerous—in fact, rarely more than one or two such cells could be seen in a high-power field.

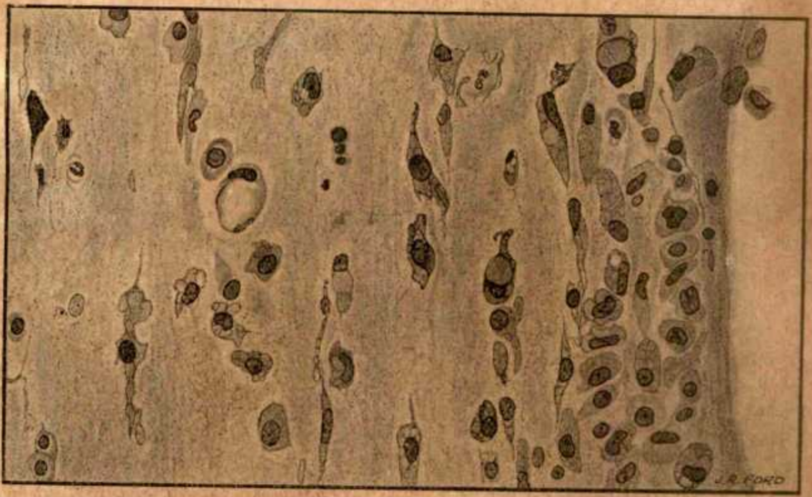


FIG. 5.—Phagocytic cells in a perivascular zone of demyelination as seen when stained by Hortega's microglia method. The cells nearer the lumen of the vessel are more rounded and contain obvious lipoid granules. Those further out are more elongated or irregular in shape.

Bielschowsky's method showed that there was little destruction of the nerve-fibres in the demyelinated areas, but the individual nerve-fibres were not free from pathological changes. The commonest abnormality was the presence of fusiform swellings and, in a few, swellings of more irregular shape so that the fibres looked like gnarled roots. The neurofibrils of the nerve-cells in the cortex and basal ganglia and the general arrangement of the fibres in the cortex as shown by this stain appeared to be normal.

Discussion of Pathological Changes.

Before discussing the significance of the pathological changes in this case it is necessary to compare them with the findings at other post-mortem examinations. Barlow and Penrose were especially struck by the hæmorrhagic nature of the disease in the cord. "Examination of the cord shows that the changes are entirely vascular in character, that they are universally distributed, but of greater intensity in some regions than others. There is great engorgement of the vessels, most of the veins being many times their normal calibre and crammed with corpuscles. Many vessels are surrounded by *a zone of coagulated exudation and beyond this for a considerable distance the tissues are infiltrated with leucocytes, giving the appearance in transverse sections of a series of concentric rings.* (Italics ours.) Beyond extensive diapedesis there is further evidence of the severity of the congestion, shown by rupture of vessels with subsequent slight interstitial hæmorrhage. The portion of the cord which had suffered most was the upper dorsal region which was so soft that it was impossible to make sections of it. Throughout, the anterior cornua have been most affected, as it is chiefly in them that the hæmorrhages are to be found, but vascular changes in other parts are nearly as great, and moreover are not confined to the cord, for in both anterior and posterior nerve-roots the vessels are much engorged."

The zones of coagulated exudation and concentric rings of exudation of leucocytes which they describe would serve very well as descriptions of the lesions in our case had we not had the advantage of more modern methods of staining than were known in 1886. The drawings and photograph which accompany their paper show quite plainly zones of perivascular change running out along the veins of the white matter of the cord, and surrounding a vessel in the region of the vagus nucleus. They note that the most affected region, about the sixth thoracic segment, was so softened that they could not cut sections from it. Unfortunately I have not been able to see the original sections, and therefore can only interpret the findings from the report and the illustrations, but I have little doubt that what they saw were zones of perivascular demyelination with multiplication of microglial nuclei which they interpreted as mononuclear leucocytes.

The brain and cord of Bergenfeldt's second case (1924) were examined by Sjövall. This was a boy, aged 6, who had measles with the appearance of the rash on March 30. On April 2 he had difficulty in passing urine and pain in the lower part of the abdomen. On the following day he was apathetic, and did not react when spoken to. His head was retracted and his neck stiff. Kernig's sign was positive. His legs were rigid and paralysed. The arms were normal. The abdominal reflexes were absent, the knee and ankle jerks reduced, Babinski negative. On April 5 he was in a condition of opisthotonus, with flaccid legs and positive Babinski signs, and he died on this day. Sjövall found no changes in the brain or meninges, but throughout the grey matter of the cord, especially in its lower segments, there were fat granule cells in the tissues and cells with larger fat droplets in the walls of the vessels. There was also a patchy perivascular infiltration. No mention is made of the distribution of the fat granule cells or of the condition of the myelin sheaths round the vessels, and it is somewhat difficult to interpret this report in relation to what has been found in other cases. But it is evident that it was a demyelinating form of myelitis and not poliomyelitis. Sjövall describes the condition as a "toxic myelitis."

Mosse's first case was a girl, aged 5½, who had measles on December 6, 1925. By the 11th she was well with a normal temperature. On the 12th she was again ill, stuporose and feverish. On the 13th she vomited and was comatose, not reacting to any stimulus. Trismus was present, the pupillary reactions were abolished, the tendon jerks and the abdominal reflexes were absent, and Babinski's sign positive. On the 15th she passed into very deep coma and died. At the post-mortem examination broncho-pneumonia was found in the right lung and congestion, with much œdema, in the brain.

In a further examination of the brain Guillery found severe œdema, and an unusual amount of lipoid in fine droplets in the cells of the adventitial sheaths and to a lesser extent in the protoplasm of the neuroglia cells.

His second case was in a boy, aged 5½. Measles succeeded tonsillitis and whooping-cough, but four days later he was well. On the seventh day after the rash he became irritable and cross, and had retention of urine. The next day the condition was the same with, in addition, incontinence of fæces. On the ninth day after the rash he was somnolent, but could be wakened. The abdominal reflexes were absent. Babinski's sign doubtful. Neither Kernig's sign nor stiffness of the neck was present. On examination in hospital two days later he was comatose and incontinent, but resented examination. *Tache cérébrale* was present. The pupils did not react to light. The muscles were hypotonic, the knee-jerks increased, and the plantars flexor in type. On lumbar puncture 70 c.c. of fluid came out in a stream. It contained no excess of cells or protein. The next day he was less comatose and was conscious of his surroundings. The pupils reacted slightly to light. Kernig's sign and stiffness of the neck were now present. He then became again more comatose and had tonic and clonic spasms of the masseter muscles. He died fifteen days after the appearance of the rash and eleven days after the onset of nervous symptoms.

On post-mortem examination there were found capillary bronchitis and congestion of both lungs, and œdema and congestion of the brain. Hæmorrhages were found on the inner surface of the dura mater, under the endocardium and in the pelvic peritoneum. Further examination of the brain was entrusted to Creutzfeld, who found no evidence of inflammatory infiltration except round one vessel. There was, however, considerable evidence of degeneration of myelin sheaths with numerous fat granule cells (Körnchenzellen) in areas around the vessels and collections of similar cells in the perivascular spaces. The white fibres of the corpus striatum and of the internal capsule were especially degenerated. In the degenerated areas the axis cylinders were also affected to some extent, and there was a definite overgrowth of neuroglia fibres. Various changes were also found in the nerve-cells of the cortex. Creutzfeld interprets his findings as "a true degenerative process in the central nervous system, affecting especially the white matter underlying the cerebral cortex. The degeneration of the myelin is clearly dependent on the distribution of the vessels, but has not the circumscribed, patchy formation seen in disseminated sclerosis. It resembles more closely the so-called *encephalitis neonatorum* of Virchow. . . . No hæmorrhages were found in the brain."

Winnicott and Gibbs (1926) record a fatal case under the care of Dr. Geoffrey Bourne, in which symptoms of encephalitis came on two to three weeks after the onset of measles. The patient, a girl aged 4, became irritable and developed twitching and rigidity. There was an excess of lymphocytes in the cerebrospinal fluid, but no tubercle bacilli were found in it. At the post mortem a "grossly hæmorrhagic type of acute encephalitis" was found.

A pathological examination was made by Siegmund on Case 10 of Brock's series (1926). This was a child aged 6, who, four days after measles, became soporose, did not pass urine but passed fæces involuntarily. The muscles were flaccid and there was no stiffness of the neck, but slight clonic movements of the arm and neck. A lumbar puncture was done which gave a cerebrospinal fluid under 290 mm. pressure, containing 170 cells per cubic millimetre and slight protein excess. She died on the twenty-third day after the onset of nervous symptoms, having remained unconscious during the whole of this period. Examination of the brain showed the white matter to be soft and of a reddish colour on section, with numerous small irregularly edged, softened flecks of a yellowish-red colour scattered throughout. These were present also in the cerebellum and pons, but were most numerous under the cerebral cortex. The smaller flecks merged into larger irregularly edged areas. Histologically all were similar, containing a congested central vessel with a ring of softened tissue round them. In these perivascular zones swollen neuroglia cells and foamy cells were abundant. Weigert-Pal and Scharlach sections showed complete degeneration of the myelin in these areas with abundant fat granule cells not only in the tissues but forming a sleeve round the vessel in the Virchow-Robin spaces. The axis cylinders, however, were very little affected. *No mesodermal reaction* was found. Siegmund describes the condition as "an acute patchy periaxial encephalitis," and compares the lesions with those of Schilder's disease. But Brock comments that the case was *clinically an acute meningo-encephalitis.* This case had a longer history than any of the others of which full pathological reports are given, and this may account both for the large size of the perivascular zones and for the absence of mesodermal reaction. It is interesting that a pink appearance of the white matter was noted on section of the brain similar to that seen in our case.

Musser and Hauser (1928) made post-mortem examinations of eight cases. No detailed notes are given either of the clinical course or the pathological appearances of individual cases, but they found, generally, lesions similar to those of encephalitis lethargica. They also note that the cut surface of the brain had a distinct pink hue. There was vascular congestion with discrete punctate hæmorrhages, and some areas of more diffuse hæmorrhage. Low-pressure hæmorrhages into the perivascular space of His were also found, apparently fairly commonly. There was also intense perivascular infiltration with lymphocytes of the smaller vessels of the brain and occasionally more diffuse infiltration with round cells. They noted macroscopic "areas of softening," but considered that these were due to hæmorrhage. Their pathological report is short and incomplete, and they do not state what staining methods had been used, but it does not appear as though any areas of perivascular demyelination had been present in their cases. It is possible that those which showed the most evident microscopic changes were cases of encephalitis lethargica and that the slighter changes of true measles encephalitis were missed.

Through the kindness of Dr. Perdrau I have had the opportunity of examining some sections of American cases which he received from Dr. Kreider, of the Willard Parker Hospital, New York. In these the lesions were practically identical to those found in our case but there was less exudate in the Virchow-Robin spaces and rather wider zones of demyelination. Probably they were from cases of rather longer standing.

Wohlwill (1928) described two cases with histological examinations of the nervous system. His first patient was a girl, aged 4, in whom symptoms of encephalomyelitis set in four days after the appearance of the measles rash. On examination she was soporose, but breathing peacefully, with no stiffness of the neck. Myoclonic movements of the arms were noted which increased on pressing on the upper arm. There was flaccid palsy of the lower limbs with very weak knee-jerks, absent ankle-jerks, and positive Babinski sign. The temperature was 105° F., the pulse 130. The blood-count showed a leucocytosis of 27,000 per cubic millimetre. Lumbar puncture gave a fluid under normal pressure (120 mm.) containing 400 cells per cubic millimetre and excess of globulin. Examination of the ears revealed no local disease. Three days later the child was comatose and incontinent. On lumbar puncture the fluid was found to contain 23 cells and gave weak globulin reactions. Signs of broncho-pneumonia appeared in the chest, and she died four days after the onset of nervous symptoms. On post-mortem examination broncho-pneumonia was found in both lungs with fibrinous pleurisy overlying it. Otitis media was present on the right side. Clots were found in the superior longitudinal sinus and in the right cavernous sinus, as well as in some of the veins of the convexities of the hemispheres. The whole brain was hyperæmic and the pia-arachnoid was injected with small areas of hæmorrhage, but there was no purulent infiltration. In the cord, especially in its lower half, there was also hyperæmia of meninges and grey matter, and a punctiform hæmorrhage was found in the dorsal columns in the lower thoracic region.

Microscopically, areas or zones of demyelination and neuroglia change were seen in three situations:—

(1) Under the pia mater of the spinal cord throughout its extent, and forming at every level a complete, though unequally wide, ring.

(2) A less regular and complete subependymal band. The ependymal cells were lost wherever this band was present.

(3) Narrow zones round distended veins throughout the nervous system.

In the cord these zones could be followed out from the grey matter to the surface along the veins of the vasa corona. In the brain it was found by examining serial sections that the affected veins were affected throughout their length, or, at least, as far as they could be traced. They did not run into and out of areas of demyelination as in disseminated sclerosis. These zones of demyelination were never as wide as the veins they surrounded. They were most numerous in the subcortical white matter, but affected a large proportion of the veins throughout the brain and brain-stem and a smaller proportion in the cerebellum. The inner layers of the cortex were also affected, but the outer layers seemed to be spared. The process was characterized by recent destruction of "nervous substance" with a "stormy neuroglial reaction." Very fine fat droplets were found in many of the swollen cells around the vessels both outside and inside the Virchow-Robin spaces. The axis cylinders in the softened areas had undergone some degenerative changes, but were much less damaged than the myelin sheaths. There was in this case no mesodermal reaction at all. No more round cells were found in the perivascular lymph spaces than are commonly seen in normal brains.

Wohlwill's second case was that of a 4-year-old girl, in whom stiffness of the muscles of the face and of the extremities came on six days after the measles rash. The next day she was stuporose with rigor-like shaking of the limbs. Kernig's and Babinski's signs were positive on both sides. Two days later, that is nine days after the appearance of the rash, she passed into deep coma with absent tendon-jerks, and died after an epileptiform attack. At the post-mortem examination fluid blood was present in the subarachnoid space over the pons and medulla and in the large cisterns. The brain itself appeared congested. On section of it, perivascular areas similar to those in the first case were found. These were most numerous in the posterior and upper parts of the cerebrum. In the brain-stem they were less abundant than in the previous case, and the cord margin was only affected over the antero-lateral tracts in the cervical region. But there was more diffuse affection of the grey matter of the cord resembling confluent areas around the numerous vessels. On the whole, the areas were larger and of looser texture, and their edges were less well defined. In addition there was in this case perivascular infiltration with lymphocytes and plasma cells in the Virchow-Robin spaces of both arteries and veins, affecting a few vessels round which no areas of degeneration could be seen, as well as practically all those which were surrounded by such areas. This infiltration was never more than one cell thick, and often formed an incomplete ring. Many of the cells of the vessel walls were degenerated; karyorrhexis was seen in some, and macrophage cells containing nuclear fragments were also found. The fat granules in the cells in the degenerated area were in this case rather larger than in the last, and some typical fat granule cells could be seen. The changes in the ganglion cells were also more severe, and various stages of degeneration and destruction were observed in them, with considerable satellitosis of the nerve-cells and of their processes, but no true neuronophagy.

It has been noted that three chief types of pathological change were present in our case (1) *congestion and hæmorrhage;* (2) *perivascular infiltration;* (3) *perivascular demyelination.* Of these the first is the most constant and has been noted in almost every case. In several cases special mention has been made of the pink colour of the centrum ovale on section. In some cases hæmorrhages have been noted on macroscopic examination, either in the meninges or into the tissues of the brain or cord. In other cases, as in ours, the hæmorrhages were of microscopic size. In all there has been either macroscopic or microscopic evidence of more hyperæmia than could be accounted for by the manner of death or the changes in other organs.

(2) *Perivascular infiltration* on the other hand has been very inconstant. No definite note is made of it in Barlow's case but it is seen in his illustrations. In Bergenfeldt's case it was present in patchy form. Musser and Hausser described it as "intense." In Wohlwill's second case, as in ours, it was discrete, the perivascular rings being rarely more than one cell thick. But at the same time it was, in our case, the most obvious pathological feature. In other cases it has been either limited to one vessel (Mosse-Creutzfeld) or completely absent (Brock-Siegmund, Wohlwill).

(3) *Perivascular zones of demyelination* have been present in so large a proportion of the cases that they must be considered as one of the most characteristic changes in the disease. By far the best description of these zones is that given by Wohlwill, who has shown that they run for considerable lengths along the smaller veins both of the brain and spinal cord. Although in the brain it was not possible to trace the whole length of any vein, he was unable to see any point at which a vein passed into or out of a zone of demyelination. Similar perivas-

cular zones are figured by Barlow and Penrose and are described by Creutzfeld in Mosse's case and by Siegmund in Brock's case.

It has already been said that this appearance is similar to, if not identical with, the characteristic change described by Turnbull and McIntosh, Perdrau and others in post-vaccinial encephalomyelitis. Although in the latter disease it is not usually seen at so early a stage as it was in our case, the descriptions of cases of equal duration of post-vaccinial and measles encephalomyelitis are practically identical. There is perhaps, in post-vaccinial encephalitis, a tendency toward more intense perivascular infiltration and more complete myelin destruction than in the measles cases. Plasma cells also appear to be more common after measles than after vaccination, but these are differences of degree rather than of kind. Certainly perivascular infiltration is as capricious in post-vaccinial as in measles encephalomyelitis. In one case which I examined it was almost completely absent, and was certainly less obvious than in our case of measles encephalitis

It is interesting to note in this connection that zones of demyelination around the margin of the cord and along the walls of the ventricles, similar to those found in Wohlwill's first case of measles encephalomyelitis, have been described by Schürmann in a case of post-vaccinial encephalomyelitis. This finding not only adds to the otherwise remarkable similarity between the pathological pictures of the two diseases, but also relates it to that of disseminated sclerosis, although the similarity to this disease is much slighter. It also conveys the suggestion that the demyelinating agent (virus, enzyme, toxin, or whatever it may be) may attack the nervous system from the side of the cerebro-spinal fluid channels and not, as has often been supposed, directly from the blood-stream.

The pathological similarity between post-vaccinial and measles encephalomyelitis corresponds with an equal similarity on the epidemiological and clinical sides. It has been seen that the periodical incidence of nervous sequelæ after measles resembles that after vaccination; both have become much more common during the past few years. Towards the end of last century nervous sequelæ were not uncommonly observed after small-pox as well as after measles. Thus Pierre Marie in 1895 stated that numerous cases of nervous sequelæ resembling insular sclerosis were observed in the convalescence from "measles, scarlatina and *above all* small-pox." "At times these symptoms cease and entirely disappear, but they may also continue and confirmed insular sclerosis occur." Such a case, occurring after measles, was described in

1892 by Dawson Williams, but the absence of remissions or of definite progression of symptoms makes us class it now as a case of the cerebellar type of measles encephalitis. It is of interest also that in Lucas' case of measles paraplegia a similar paraplegic attack had come on previously after small-pox. There is of course the possibility of hysteria in this case, but the similarity of the symptoms to those in other cases of measles paraplegia are against this hypothesis. This case of itself affords strong support for the view, which has been put forward on other grounds by Bastiaanse and Perdrau, that both the post-vaccinial and other forms of encephalitis which follow eruptive fevers are not directly due to the virus of the preceding fever, but to another virus which is either stimulated to activity or is directed against the nervous system by the exanthem. This view is certainly consonant with the epidemiology of the encephalitis of measles. A condition which occurs in so small a proportion of cases of measles and which in one year may suddenly appear with much greater frequency and cause more deaths than in the previous twenty years, is unlikely to be due to a sudden change in the nature of so common a disease. It is much more likely to be due to some other concurrent epidemic which does not produce much obvious effect unless the carrier of the virus is attacked by small-pox or measles.

CEREBROSPINAL FLUID.

Little help must be expected from an examination of the cerebrospinal fluid in the differential diagnosis of measles encephalitis, as the characters of the fluid obtained in this disease have been very varied. In many cases the fluid has been normal. In others, clinically not more severe, a great increase of cells, up to 400 or over, and excess of protein and globulin has been found. The cells are usually mononuclear, and we may perhaps question the diagnosis of the few cases in which the fluid has been turbid from the presence of polymorphonuclear cells; but the first case quoted by Musser and Hauser indicates that polymorphonuclears may be present early in the disease, and may later be replaced by mononuclears. In the fluids which I examined the cell count was never high (6, 15, 31 per cubic millimetre), and was purely mononuclear. Neal and Appelbaum, in their twelve cases, found from three to eighty-seven cells of mononuclear type. A curious discrepancy is apparent in Wohlwill's first case between the high cell count (400 per cubic millimetre) obtained four days before death and the complete absence of perivascular or meningeal infiltration in the brain and cord on post-mortem examination. It is possible that the drainage of cerebrospinal fluid by the two lumbar punctures emptied the Virchow-Robin spaces of their cellular infiltrations. It is noteworthy that in the fluid obtained by the second lumbar puncture the cells had dropped to 23 per cubic millimetre.

The protein and globulin are usually in excess even when no cells are found, and they appear to increase more or less proportionately with the cell count, but the number of cases in which a careful examination of the cerebrospinal fluid has been made is much too small for any certainty on this point. It appears, however, that "cell-protein dissociation" (a high cell count with normal protein), which is so common in encephalitis lethargica, is not found in the encephalitis of measles. The data as to the other chemical examinations are still more scanty. In the two fluids of which I made full chemical examinations the chlorides were normal; the glucose was high normal in one and in excess in the other. Neal and Appelbaum also found the glucose content normal or increased.

The pressure is often high. Bergenfeldt, Brock and Lust obtained readings in the neighbourhood of 300 mm. in some cases of encephalitis, but in others more normal readings were obtained (Lust 120 and 160 mm., Bergenfeldt 160 mm., Brock 170 mm.). Mosse found an excess of pressure in both of his cases; in his second case the fluid came out in a stream, and 70 c.c. were rapidly collected. Neal and Appelbaum also found the pressure increased. Practically no data are available as to the pressure in cases of myelitis. It is difficult to understand why normal pressure readings are sometimes found in encephalitic cases, seeing that congestion of the brain is the most constant pathological feature of the disease. At the same time the fact that the pressure is not increased may be a valuable point in distinguishing the disease from meningitis at the bed side.

Even when the pressure is raised a complete examination of the fluid will usually indicate the absence of meningitis either by the low cell count or by the normal or high percentages of glucose and chlorides. A high cell count will indicate that the symptoms are not of toxic or uræmic origin. Thus, on the whole, the chief value of the examination of the cerebrospinal fluid will be in the exclusion of other diseases rather than in giving conclusive evidence of the presence of encephalitis.

SUMMARY AND CONCLUSIONS.

(1) The encephalomyelitis which occurs in the convalescence of measles is in the majority of cases a disease clinically distinct from poliomyelitis, encephalitis lethargica, or Landry's paralysis. When recovery occurs it is usually remarkably complete.

(2) The examination of a fatal case and a review of the literature indicate that the encephalomyelitis of measles is characterized by three main types of change. (1) Diffuse congestion of the brain, especially of the white matter, sometimes causing petechial hæmorrhages; (2) a discrete perivascular infiltration with round cells (this is often absent); (3) small perivascular zones of demyelination. The last is the most characteristic change of this form of encephalomyelitis.

(3) No clinical or pathological distinction can be drawn between the encephalomyelitis following measles, and that which may follow vaccination and small pox. The epidemiological incidence supports the similarity of the two diseases.

(4) It is therefore probable that these diseases are caused by an unknown virus which spreads in epidemic waves, but produces no disease unless stimulated to activity by the exanthem.

REFERENCES.

Encephalomyelitis after Measles.

Abercrombie, J. "Diseases of the Brain and Spinal Cord," 4th edition, Edinburgh, 1845, p. 158.
Barlow, T. *Brit. Med. Journ.*, 1886, **2**, 923.
Barlow, T., and Penrose. *Med. Chir. Trans.*, 1886, **70**, 77.
Batten, F. E. *Brain*, 1904, **28**, 484.
Bergenfeldt, E. *Acta Med. Scand.*, 1924-25, **61**, 281.
Bergeron. *Gaz. des Hôp.*, 1868, p. 5.
Blasi, D. *Pediatria*, 1928, **36**, 862.
Boisserie-Lacroix, J., and Malaplate, J. *Journ. de Méd. de Bordeaux*, 1927, p. 946.
Box, C. R. *Lancet*, 1921, **1**, 222.
Branson, G. J. *Brit. Med. Journ.*, 1905, **1**, 941.
Brook, J. *Zeitschr. f. Kinderheilk.*, 1926, **40**, 552.
Carpenter, G. *Proc. Soc. Study of Disease in Children*, 1908, **8**, 338.
Comby. *Arch. de Méd. des Enfants*, 1921, **24**, 456 and 488.
D'Espine. *La Presse Médicale*, 1920, p. 617.
De Mare, F. *Pediatria*, 1927, **35**, 1182.
Elliot, E. F. *Lancet*, 1900, **1**, 583.
Ford, F. R. *Bull. Johns Hopkins Hosp.*, 1928, **43**, 140.
Guthrie, L. *Proc. Soc. Study of Disease in Children*, 1905, **5**, 13.
Hegler. In "Jochmann's Lehrbuch der Infectionskrankheiten." 2nd Auf. Berlin: J. Springer, p. 760.
Horwitt, S. *Arch. of Pediatrics*, 1924, **41**, 476.
Imbert-Gourbeyre. *Gaz. Médicale*, 1863, **18**, 418.
Ker, Claude B. "Infectious Diseases," 1920, 2nd edition, Henry Frowde, p. 51.

Liégard, A. *Gaz. des Hôp.*, 1889, p. 562.
Lowenburg-Schaller. *Arch. of Pediatrics*, 1926, **46**, 78.
Lucas, James. *London Med. Journ.*, 1790, **11**, 325.
Lust, F. *Münch. med. Woch.*, 1927, **74** (1), 96.
Mosse, K. *Jahrbuch. f. Kinderheilk.*, 1926, **112**, 272.
Musser, J. H., and Hauser, G. H. *Journ. Amer. Med. Assoc.*, 1928, **90**, 1267.
Neal, J. B., and Appelbaum, E. *Ibid.*, 1927, **88**, 1552.
Pitt, Newton. *Trans. Clin. Soc.*, **37**, 28.
Redlich, Fr. *Zeitschr. f. Kinderheilk.*, 1927, **43**, 178.
Schreiber, G. *Bull. de la Soc. de Péd. de Paris*, 1925, **23**, 337.
Smith, J. A. *Proc. Soc. Study of Disease in Children*, 1904, **4**, 177.
Todesco, J. *Lancet*, 1926, **2**, 21.
Winnicott, D. W., and Gibbs, N. *Brit. Journ. Child. Diseases*, 1926, **23**, 107.
Wohlwill, Fr. *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1928, **112**, 20.

Encephalomyelitis after Vaccination and Smallpox.

Clifton, Francis. "Dissertatio medica inauguralis de distinctis et confluentibus variolis." Lugduni Batavorum, 1724.
Freind, John. "Nine commentaries upon Fevers and two epistles concerning the small pox." English translation by H. Dale, p. 125, Cox, London, 1730.
Perdrau, J. R. *Journ. Path. and Bact.*, 1928, **31**, 17.
Schürmann, P. *Beitr. z. path. Anat. u. z. allg. Path.*, 1928, **79**, 409.
Turnbull, H. M., and McIntosh, J. *Brit. Journ. Exper. Path.*, 1926, **7**, 181.

THE BI-COLOURED GUAIAC TEST.[1]

BY DR. EUGENE DE THURZO.

Privat Dozent at the Neurological Clinic of the University in Debrecen (Hungary).

Two trends are obvious in the recent development of methods of neurological diagnosis. Clinical observers, interested in symptomatology, describe from day to day new symptoms, while those engaged in research constantly publish new methods and reactions. Critics may think that there is a certain overproduction in this direction, and accept the description of a new symptom, a new reflex, or a new laboratory method with a certain reserve; but this is a somewhat one-sided view to take.

What is the true reason for adding new signs and methods to the large number already known, even when they add little to the clinical description of a case? Without any doubt it is because in nervous diseases one wants a diagnosis as early as possible. The description of many new symptoms, which are called "petits signes" by French authors, and of many new laboratory methods, are of value for this reason. Similarly in the examination of the spinal fluid attempts are always being made to find new tests in spite of the large number already known. The colloidal reactions undoubtedly show the greatest development, as indeed these may reveal the finest physico-chemical and structural modifications of the spinal fluid. Of all the methods of examination of the spinal fluid the colloid reactions are those that earliest give changes characteristic of the disease and of pathognomonic value.

Among the advantages which the colloidal reaction has over the other methods of research are principally *its qualitative character*, its *high sensitivity* and—in a case of nervous syphilis—the possibility of obtaining a fine *differential diagnosis* by its use. In some cases the results of the colloidal reactions may indicate a certain disease even when the most careful clinical investigations do not show any abnormality. As an instance of this we may note that Mras and Landsteiner picked out in this way those syphilitics who were candidates for general paralysis.

---

[1] Preliminary note from the Pathological Laboratory of the National Hospital for Nervous Diseases, Queen Square, London.

In the clinic of Debreczen we had the opportunity of making a similar observation and we reported two such cases (in the *Deutsche Zeitschrift für Nervenheilkunde* (1925, W. 85)). In these cases no sign of general paralysis could be ascertained from a clinical examination, but the colloid reactions clearly showed that they were actually in the early stage of this disease, and in fact two and a half years later its clinical symptoms appeared.

The task of the future in the examination of the spinal fluid is not only to aid in diagnosis or prognosis, but also in the prevention of disease. And in order to do this it must show the finest and most pathognomonic alterations in the fluid even before the symptoms of the disease have appeared. As regards neurosyphilis this has already been achieved to some extent. But it may be asked: Do the colloid reactions which are already known satisfy these demands? I think the invention of new colloid reactions must have certain points in view. If we increase the sensitiveness of the colloid reactions we have to get rid of certain difficulties. Thus using a very sensitive colloid solution we may get a deviation with a normal spinal fluid on account of its normal content of protein. The already known colloid reactions cannot indeed be made more sensitive. For instance, Lange found that the "limit value" of the gold-sol test is 0·018 per cent., that is to say, this is the smallest value of protein content of the spinal fluid which the reaction can reveal; below this amount we never get deviation with the test, over it we always do. But from the data pertaining to the protein content in normal spinal fluid we see that the "limit value" in the gold-sol test is within such bounds that sometimes a normal spinal fluid is capable of causing a reaction. For that reason we need to test the composition of spinal fluid with a colloid reagent which does not altogether depend upon the total protein content. The various colloid solutions prove of different sensitivity to each protein fraction, as I have already pointed out in my book on the new colloidal methods for the spinal fluid: "Les nouvelles méthodes sur les réactions colloidales du liquide cephalorachidien." Paris, 1927).

In my own researches upon the theoretical basis of colloidal reactions I have emphasized the fact that it is not enough to speak of salt and colloid sensitivity of colloid reactions, but that it is necessary to examine separately the sensitiveness to each protein fraction, i.e., to euglobulin, pseudo-globulin, fibrin-globulin and albumin. It is only then that one can really assess the qualitative value of colloid reactions and connect the colloido-chemical alterations of structure with the different disease processes. Among the protein fractions of the spinal fluid the euglobulin has the highest pathognomonic value. Its relative increase usually indicates a syphilitic lesion of the central nervous system. For the examination of the spinal fluid we need a colloidal system which shows a special sensitiveness to euglobin and to a less extent to albumin, and which is influenced less, or not at all, by the other protein fractions. Such a colloid solution does not show a reactional deviation, even with a great increase of total protein of the spinal fluid, so long as the euglobulin is not proportionally increased. Taking into consideration these requirements, after long researches in the laboratory of the National Hospital for Nervous Diseases, with the kind help of Dr. Greenfield, I have elaborated a new colloido-chemical reaction, the bi-coloured guaiac resin test (B.G.T.) of the spinal fluid. The execution is very simple and is easily carried out in any laboratory.

Technique.—We use a compound colloid system which is composed of a mixture of a suspension of guaiac tincture and two colour solutions. That is to say, we mix a colloid of greater dispersion with two colour solutions of finer dispersion called semi-colloids. By the mixture of guaiac resin suspension with these two contrasting colours, that is to say, bi-coloration, we may obtain vivid colour differences in the test. (We shall later briefly explain the chemical process of this colloid reaction, as well as the nature of each separate component).

For the execution of the bi-coloured guaiac resin test the following solutions are necessary:—

(1) The tincture of guaiac resin, according to the *British Pharmacopœia*, containing 20 per cent. guaiac solution in alcohol.

(2) Naphthol green (G. T. Gurr, London) in 0·5 per cent. solution in distilled water.

(3) Brilliant fuchsin (G. T. Gurr, London) in 0.5 per cent. solution in absolute alcohol.

(4) Ten per cent. NaCl sol. from which we make the 0·2 per cent. solution of saline used for the series of spinal fluid dilutions.

(5) Half per cent. solution of anhydrous sodium carbonate.

The reagents can be kept for quite a long time in dark bottles with glass stoppers.

We complete the guaiac suspension in the following manner: We fill a small Erlenmeyer flask with 40 c.c. of distilled water. Then we pour with a pipette slowly along the wall of the flask a solution of 0·22 c.c. guaiac tincture in 9 c.c. absolute alcohol, during which time we lightly and continually shake the flask. Thus we obtain a suspension of guaiac resin somewhat yellowish-white, transparent and only feebly opaque to an overhead light. To this flask we now add 2 c.c. naphthol green solution, agitating it slowly with a circular motion. When the mixture of the coloured solution is completed we again add 0·3 c.c. of brilliant fuchsin solution. The guaiac resin suspension thus produced is cherry red, quite transparent, and slightly opaque to an overhead light. After twenty to thirty minutes it is ready for use. Up to that time it has shown an equilibrium between the suspended particles of guaiac resin and the colloid particles of the colour solution in the bi-coloured electrocolloid system.

For the test we make in the usual manner a series of dilutions in ten small glass tubes. We drop ½ c.c. of spinal fluid with a pipette into the first and second tubes. Then starting from the second tube we add to each tube ½ c.c. 0·2 per cent. sod. chloride, containing 1 c.c. of ½ per cent. sodium carbonate in each 100 c.c. It is convenient to prepare the 0·2 per cent. solution from the 10 per cent. solution, always fresh in the quantity desired. Beginning from the second tube we transfer, after mixing, ½ c.c. to the third tube, and so on in the usual manner. We thus obtain dilutions of 1/1, 1/2, 1/4, &c., to 1/500 of spinal fluid. We then add to each tube of the series ½ c.c. of the suspension of bi-coloured guaiac resin. Each tube has to be gently shaken.

The most suitable time for reading the result is the next day (twenty or twenty-four hours after the end of the reaction). For this purpose we examine the tubes by transmitted light, preferably with artificial light. The alterations of the tubes are indicated by a co-ordinate system or in numbers, corresponding to the following degress of reaction:—

0 (−).	The solution is unchanged, red, without precipitate.
1 (±).	The solution is of light red colour, with a slight precipitate.
2 (+).	Greyish red colour with evident sedimentation at bottom of tube.
3 (++).	Greyish green colour, red precipitate at bottom of tube.
4 (+++).	Vivid green colour, red precipitate at bottom of tube.

I have investigated spinal fluids from various diseases of the central nervous system with the bi-coloured guaiac reaction. The spinal fluids were also examined for the number of cells and the total protein content, and also for the globulin, gold-sol and Wassermann tests by Dr. Greenfield. (We will report our detailed results in a later paper, and give here only the principal types.)

In G.P.I. we obtain in the first four to six tubes the complete deviation (see fig. 1) No. 4, or +++. In tabes dorsalis, and in syphilitic myelitis, the greatest deviation shows itself mostly in tubes Nos. 2, 3 or 4 (see fig. 1). After malarial therapy we obtained a weaker paretic curve. In other nervous diseases, for example epilepsy, poliomyelitis, Paget's disease, spinal tumours with high protein content, polyneuritis, amyotrophic lateral sclerosis, non-syphilitic myelitis, cerebral thrombosis and meningism, we obtained negative results. Disseminated sclerosis may, according to our examinations up to the present time, show a certain degree of positivity, viz., 034432200. One can conclude from this that in that disease the globulin fraction represents a fairly high fraction of the protein present in the spinal fluid and that euglobulin is to be found in a definite quantity.

BICOLOURED GUAIAC TEST (B.G.T.).

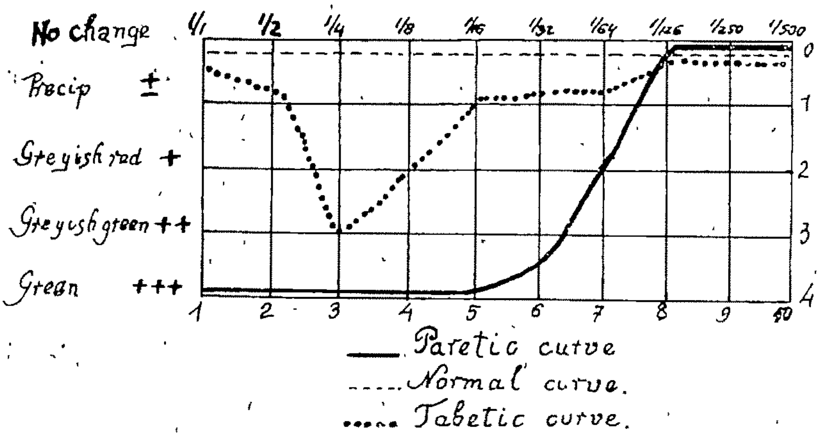


FIG. 1.

RATIONALE OF THE TEST.

In the bi-coloured guaiac suspension the guaiac colloid particles have a negative electric charge. The colloid particles of finer dispersion (naphthol green and brilliant fuchsin) are adsorbed to the guaiac particles. Naphthol green plays the rôle more of protection, and of a colloid of positive electric charge; brilliant fuchsin possesses a negative one. The saline sensitivity of the whole established colloid system is of 0·3 per cent. NaCl titre, as it was found that such a percentage of NaCl, mixed in the same quantity with the colloid solution, has a neutralizing effect.

RESULTS.

We have compared the results of the bi-coloured guaiac test with the other methods and we shall speak briefly of that. The system proves to have great sensitiveness especially in neurosyphilis. From our results there appears to be an evident parallelism, firstly, with the result of Wassermann reaction. When the latter is positive, we always obtain a positive reaction as well. With the globulin reactions there appears a parallelism only when the relative increase of the globulin fraction is quite evident. The reaction shows no real parallelism with the total protein content or quantity of cells. Even spinal fluids with high total protein content, as in a case of compression of the spinal cord or in cases of meningitis, give negative results or quite small deviations. Comparing it with gold-sol and mastic reactions we see that the bi-coloured guaiac test shows a greater sensitiveness. It has a greater relative sensitiveness for euglobulin and pseudoglobulin than for the other protein fractions, and for these we obtain a deviation principally in the left zone. In a relative sense this test has a specific pathognomonic value for neurosyphilis.

On Dr. Greenfield's initiative we have investigated the globulin and albumin fraction from a positive spinal fluid by means of the bi-coloured guaiac test. (On these researches we shall report later in detail.) During the course of the working out of this test we performed researches to see the influence of different degrees of alkalinity with potassium carbonate (2 per cent. solution) upon the different degree of the bi-coloured suspension. In brief, we can say that we can abolish with such a degree of alkalinity the deviation of the test due to the albumin fraction, whereas with the same degree of alkalinity the deviation caused by euglobulin fraction will be diminished only in much smaller degree. It is true that with the addition of alkali the deviations appear somewhat slowly. The precipitating effect of euglobulin upon the bi-coloured suspension appears also later, indicating that the whole colloid system is farther from the zone of rapid coagulation. There exists also a close relation between globulin or albumin sensitivity on the one hand, and the remoteness from the rapid coagulation zone. These facts possess no doubt a certain theoretical value and consequently also help us to know in what direction we must pursue the researches on colloido-chemical reactions for blood serum, the aim of which is to replace the Wassermann reaction. The reaction modifications appear with the bi-coloured guaiac test after five to eight hours, and it is not desirable to read the curves at the beginning. The reaction possesses, in addition to its simplicity of performance, the advantage over the gold-sol and benzoin resin reaction that the reading by strong colour contrast is easier and more objective, more certain results are obtained in neurosyphilis, and the necessary reagents are particularly easy to obtain. The preparation of bi-coloured guaiac test sols is undoubtedly simpler than that of gold-sol, and the results obtained with the former are more standard.

Some measure of critical reserve with respect to complicated and cumbersome new methods may be justified. Probably Billroth was quite right when he said: "Diagnosis in medical science is difficult only because there are many professors, lecturers and other physicians who know so well how to complicate the simplest things, and to make them harder to understand by beautiful descriptions."

The aim of this new method, however, is not to complicate the examination of the cerebrospinal fluid, but rather to offer for practice a simple procedure. Numerous further researches are needed before its true value can be established, as with the other colloid reactions. But it already appears without any doubt that in the diagnostics of the spinal fluid the precept, "Experimentum docet, theoriae variunt," authorizes further researches in the field of colloid reactions.

A CLINICAL STUDY OF AN HEREDO-FAMILIAL DISEASE RESEMBLING DISSEMINATED SCLEROSIS.

BY FERGUS R. FERGUSON

AND

MACDONALD CRITCHLEY.

From The National Hospital, Queen Square, W.C.

THE object of this contribution is to record the clinical details of an heredo-familial affection which, as far as we can trace, is not mentioned in the literature. There are already on record a large number of cases of peculiar familial affections which do not conform to any particular well-defined clinical group; on the other hand there is a striking lack of exact knowledge as to the pathological basis of some even of the better demarcated clinical syndromes. The excuse for adding to the already over-burdened clinical data without corresponding anatomical support lies first in the large number of cases afflicted in this particular family. Most of the atypical cases on record concern two—or at most three—members, but here we are dealing with no fewer than thirteen affected individuals belonging to one family. Throughout this family the clinical picture is uniform; such differences as exist being of degree rather than of kind.

The second noteworthy point in this family is that several of its members have at various times been diagnosed as suffering from disseminated sclerosis; consequently this paper may serve to throw some light on the problem of so-called familial disseminated sclerosis.

We would like to take this opportunity of thanking Dr. Grainger Stewart under whose care at the National Hospital two of the patients were admitted.

The Drew family of Walworth comprises a large number of individuals, many of whom we have examined personally. Concerning some of the others, we have been able to refer to detailed notes. We know with certainty that the affection involves at least two generations. We have no certain knowledge as to the more remote ancestry except that there was an inter-marriage of cousins two generations before the first known affected line.

The opportunity for this inquiry was the admission to hospital of one member, namely, Mrs. C. P. Inquiry into the family history led to the discovery of a similar affection amongst thirteen members of the family.

As far as we have exact knowledge the disease started in two brothers whom we have referred to as Generation A. Amongst the predecessors it appears that one—if not two—were also similarly affected, but we have been unable to trace details of these.

Generation A (see genealogical tree).

No. 1.—W. D., male, aged 40, was admitted to the National Hospital under the care of Sir William Gowers in 1895. He complained of pains in the back, tingling in the hands, and of weakness and unsteadiness of the legs of a year's duration. Tremors in the hands had appeared five months previously, and were accompanied by intense thermal dysæsthesiæ in the lower limbs. Except for typhoid and gonorrhoea he had always enjoyed excellent health; syphilis was denied. Physical examination revealed a well-nourished man with a rather expressionless, melancholic facies; there was a peculiar tremulousness around the angles of the mouth on speaking. His speech was drawling, monotonous and badly articulated. The mental state was fairly good. The optic discs were normal; the pupillary reactions and the ocular movements were normal but there was a fine, rapid nystagmus on lateral deviation. There was no diplopia at the time of testing although he had previously complained of transient double vision. The other cranial nerves were healthy except for some tremor and weakness of the tongue. All movements of the right upper limb were weak and there was definite weakness of legs and trunk. His hands were tremulous. No objective sensory loss could be demonstrated. The abdominal reflexes and knee-jerks were normal but no plantar responses could be obtained; there was no ankle clonus. His gait was slow, cautious and shuffling; and he tended to fall backwards and to the right. Rombergism was marked.

The patient remained in hospital five months and was discharged with the tentative diagnosis of paralysis agitans.

Three years later he was admitted to Southwark Infirmary where he died a year afterwards from pneumonia and gangrene of the lung. The post-mortem records state that the brain and spinal cord showed no macroscopic changes, but a histological examination was not carried out

No. 2.—H. D., male, was born in the year 1864. Unfortunately we have no clinical details of this case, but we learn from his relatives that for about ten years before his death he was slowly becoming paralysed. During this time they noted that his speech was slow and almost unintelligible and that his face was vacant and his eyes fixed. For the last five years of his life he was bedridden. He died at the age of 49 in Camberwell Infirmary where he had been an inmate for ten years. No autopsy was performed.

No. 3.—C. D., female (sister of Nos. 1 and 2). No certain details of this person are available; she is said by some to have been affected, but the majority of the family deny this. It is certain, however, that she died from carcinoma of the breast at the age of 44.

Generation B comprises the offspring of these members; W. D. had ten children including seven males and three females (see genealogical tree).

No. 4.—W. J. D., male, the eldest child of W. D., was born in 1878. His symptoms first appeared in 1918 with progressive weakness of the legs, followed twelve months later by numbness and pains in the legs. Four years later he complained of tremor of the legs and weakness of the hands. At this period he was admitted to St. Thomas's Hospital where the diagnosis of heredo-familial ataxia was made. Two years after leaving this hospital he developed diplopia and hesitancy of micturition. At the same period his relatives noticed that his speech was very slurred. In 1926 and again in 1927 he was admitted to the Lambeth Infirmary where he was regarded as a case of disseminated sclerosis. He was admitted to the National Hospital in October, 1928, under the care of Dr. T. Grainger Stewart. Examination revealed him to be a well-nourished man with a vacant, staring facies and a variable lid retraction. His speech was lalling and dysarthric; temperamentally he was facile and euphoric and exhibited pathological laughter. Investigation of the cranial nerves revealed temporal pallor of each optic disc. Upward and lateral movements of the eyes were defective and gave rise to diplopia. Nystagmus was present. Tonus was normal in the arms but was obviously increased in the proximal parts of the lower limbs and was accompanied by involuntary flexor spasms: the distal portions of the legs were, however, distinctly hypotonic. A rhythmical tremor of Parkinsonian type was present in the trunk, head and more particularly in the lower limbs. Motor power was good; co-ordination tests well performed in the arms and legs. Sensory examination revealed a loss to pin-prick and thermal sensibility over his legs and trunk and a diminution in the arms. Vibration sensibility was absent at the wrists and ankles, and postural sensibility was defective in the toes. The arm-jerks were normal, the knee-jerks present and ankle-jerks absent; the abdominal responses were obtainable and plantar stimulation evoked an extensor type of response. He was unable to walk without assistance; Rombergism was well-marked. The blood-Wassermann reaction proved negative.

No. 5.—H. D., male, born 1881. He died in Canada in 1925 in the Chatham General Hospital, Ontario, at the age of 44. The only information obtainable is that for some time (about five years) prior to death he lost the use of his arms and legs and had difficulty with his speech. He then became emaciated and bedridden. Although clinical details from the hospital have not been forthcoming, we are able to quote the diagnosis made by Dr. Northwood, who attended him: "Blood examination" he writes, "showed a positive Wassermann reaction; spinal fluid was not examined, and no autopsy was performed. The diagnosis in this case was Lues with Locomotor Ataxia, although the symptoms were certainly not typical."

No. 6.—J. D., born 1882. His health was always good until January, 1927, when, as the result of an accident, he was admitted to Guy's Hospital suffering from a fracture of the radius and of the patella. After his discharge from hospital in July, 1927, he complained of weakness in the legs, especially the left. At the same time he noticed some difficulty in his speech. When examined in December, 1928, he showed a definite Parkinsonian facies with a staring appearance. His mental attitude was one of depression; the speech was monotonous, slow and slurring. There was no optic atrophy; ocular movements were full in a downward and lateral direction but were definitely defective in an upward direction; nystagmus was present on looking to the left and right. Bilateral lid retraction was a prominent feature. Tremor was visible in the face and tongue, and he made frequent smacking and sucking movements with the lips. Examination of the motor system revealed a definite poverty of movement and a tendency to assume fixed attitudes. There was a fine tremor of the outstretched arms, but no ataxia or intention tremor was demonstrable. Motor power and tone were normal in the arms. Apart from weakness in the left leg—the result of the accident—there was no abnormality observable in the lower extremities. No sensory change was present with the exception of an indefinite hypalgesia over the legs. The ankle-jerks were absent; plantar stimulation gave a sluggish flexor response; other reflexes were normal. His attitude in walking was one of flexion; he did not swing his arms, and progression was slow. Slight Rombergism was present.

There was a delay in the healing of the wound following wiring of the patella; the blood-Wassermann was, therefore, examined at Guy's Hospital and found to be strongly positive. The patient was unwilling to undergo further investigation.

No. 7.—C. P.[1] (*née* D.), female, aged 45: born in 1884. Her symptoms appeared nine years previously and consisted in unsteadiness in walking; at the same time her legs felt heavy and weak. Her symptoms grew worse, and two years ago she first noticed some difficulty in talking; weakness of the hands appeared twelve months ago, and for six months there had been dysæsthesiæ in the arms and legs. For two years she had numerous attacks of mistiness of vision, and for a year there had been transient diplopia. Micturition had been precipitate with occasional incontinence since a confinement two years ago. The previous health was uneventful.

She was admitted to the National Hospital, Queen Square, in September, 1928, under the care of Dr. Grainger Stewart. Examination revealed a well-nourished patient with nothing abnormal in her facial appearance. Her psychical state was marked by a definite euphoria, there was no intellectual defect. The speech was indistinct, deliberate and hesitant. The pupils were normal; there was a defect in upward deviation of the eyes and a fine rapid nystagmus appeared when she looked in a lateral direction. The cranial nerves were otherwise normal. The optic discs were natural. A definite intention tremor was revealed by the finger-nose and heel-knee tests Motor power was good; tone was somewhat increased in proximal parts of the legs, while the distal portions were distinctly hypotonic. The tendon-jerks were everywhere brisk; abdominal responses were not obtainable: plantar stimulation gave very slight responses of the extensor variety. There was a diminution to pin-prick, heat and cold over the trunk and extremities, especially on the left side. Vibratory and postural sensibility were diminished in both legs. The gait was ataxic, and there was well-marked Rombergism. Both feet were in an attitude of pes cavus; there was no scoliosis.

---

[1] This patient together with No. 4 were shown before the Meeting of the Neurological Section of the Royal Society of Medicine (8) held on November 8, 1928.

No. 8.—T. D., male, born 1886. He was quite well until two years ago, when he noted a gradual onset of weakness and unsteadiness of both legs For eighteen months he had complained of some difficulty in speaking and transient diplopia to the left, his previous health had been good. Slight slurring speech was noted on examination; the facies was normal. The optic discs were definitely pale and nystagmus was present on upward and lateral deviation. Upward movement was defective, especially in the right eye. Lateral deviation was also poor, and he had diplopia on looking to the right and left. Pupils and fields of vision were normal. There was no abnormality in the functions of the other cranial nerves. The power of the arms was good; the tone was normal, and there was no inco-ordination. Apart from some slight weakness in the dorsiflexors of the feet the lower extremities were normal. The tendon-jerks were normal and the abdominal reflexes were present Plantar stimulation gave a slight flexor response on the right side and no response on the left There was hypæsthesia over the dorsum of the left foot; vibration sense was diminished in both legs, and to a less extent in the arms; postural sensibility was impaired in the proximal joints of the upper extremities and in the left leg; otherwise sensation was normal He walked on a broad base, swaying slightly from side to side; Rombergism was well-marked.

No. 9.—J. D, male, born 1888. This member has at no time complained of any symptoms referable to his nervous system, and complete neurological examination failed to reveal any abnormality whatever.

No. 10.—R. D., male, born 1890. This member died at the age of 12 months from convulsions.

No. 11.—J. D, female, born 1894. This individual lives in Canada; she has written to say that she is perfectly well and has recently been examined medically, and no abnormality found.

No. 12.—M D., female, born 1896. She died at the age of a few months from convulsions associated with teething.

No 13.—H. D., male, born 1898. For the past two years he has noticed a slight unsteadiness in walking, especially at night-time, but he has never fallen. There are no paræsthesiæ and no unsteadiness of the arms. When examined in November, 1928, we found a small irregular crescent of pallor just beyond the temporal margin of the disc; the cranial nerves were normal Apart from very slight weakness of the left leg the extremities were normal in every respect. There were no changes in the reflexes, but it was noticed that the plantar responses were feeble. Rombergism was present in a slight but definite degree. The speech was slightly hesitant. his brother had noticed that recently he had a tendency to stutter, and also that he was less steady on his feet.

The children of H. D. (No. 2) may be considered at this stage. There were five in all, comprising three females and two males.

No. 14.—A. D. (*née* D.), female, born 1882 (*circa*). This member died at the age of 40 from influenzal pneumonia. Her sister tells us that she was walking up to the day prior to her death, but that for one year previously she had experienced difficulty in walking, and frequently fell. As far as she knew, there was no abnormality of the vision or speech.

No. 15.—E. C. (*née* D.), female, born 1884. This woman died from pulmonary tuberculosis at the age of 30. So far as we can trace there was no indication that she was not in good health apart from symptoms referable to the chest.

No. 16.—H. D., male, born 1888. This man served in the Indian Army for eight or nine years prior to the War. He was discharged about 1915 because of unsteadiness in the legs, difficulty in speech and tremulousness. He was admitted to a military hospital and discharged thence as incurable. His sister, who gave us this information, has not seen him for six years, but says that at that time he was practically helpless. We have been unable to get in touch with this patient but as far as we know he is still alive.

No. 17.[1]—E. D., female, born 1889. At the age of 21 her walking became unsteady and she noticed a tendency to fall forwards. Her legs dragged and after going a few yards they became very stiff. A year later she began to suffer from diplopia and blurred vision. At the same time she first noticed a difficulty in swallowing and her voice became hoarse and her speech jerky so that people could no longer understand her. Micturition became precipitant and occasionally there was incontinence. Dysæsthesiæ were complained of in the arms and legs; she also complained of vertigo, dyspnœa and a stridulent cough. Her previous health had been excellent. This woman was admitted to the National Hospital, Queen Square, under the care of Dr. James Collier, in May, 1913. The notes describe her as a healthy looking girl of moderate intelligence but distinctly euphoric. Speech was extremely slow and dysarthric. Slowness of cerebration and inattention somewhat restricted the examination. The fields of vision seemed to be peripherally restricted. Optic discs were pale especially on the left side. Diplopia occurred on lateral and upward deviation, and there was some weakness of both external recti muscles. An irregular, horizontal nystagmus was present on lateral movement of the eyes. The pupils were normal. Slight weakness of the right face with perioral tremor was evident. Palatal elevation was oblique, and the tongue was protruded slightly to the right. There was a fine tremor of the out-stretched hands and all movements were a little unsteady; this was especially seen in a clumsiness of fine finger movements. There was no intention tremor and the tone and power were normal. Dorsiflexion at the ankle joints was distinctly weak and there was slight feebleness at all joints in the legs. The tone was definitely increased in the lower extremities and co-ordination tests were awkwardly carried out, although there was no ataxia or intention tremor. There was no tremor at rest but a good deal of irregular tremor was exhibited on testing the motor power of the limbs. The retarded cerebration considerably restricted the examination of the sensory system, but there appeared to be definite diminution to all forms of sensation in the legs and lower part of the trunk. All the tendon-jerks were brisk and the plantar responses were extensor. The abdominal reflexes were present. The gait was very unsteady Romberg's sign was not present.

---

[1] This patient was demonstrated before the Clinical Meeting of the International Congress of Medicine, 1913.

After her discharge from the National Hospital the patient was admitted to an infirmary where she died at the age of 28, i.e., seven years after the onset of symptoms. No details of the autopsy are available.

No. 18.—M. N. (*née* D.), female, born 1890. This member was seen by us in November, 1928. She made no complaint of any neurological symptoms and complete examination showed no abnormality whatever.

Lastly the children of Mrs. C. P. remain for investigation. We have details of seven, namely three females and four males.

No. 19.—H. P., male, born 1873. Symptoms commenced at the age of 43, i.e., twelve years previously, with a gradual onset of weakness in the legs and difficulty in walking. He gradually became more incapacitated and attended the out-patient department of King's College Hospital, where he was seen by Dr. Kinnier Wilson, from 1924 to 1926. In 1927 he had an attack in which he suddenly became unconscious, his eyes were staring; he frothed at the mouth, the head was thrown back and the arms and legs were rigidly extended. He was incontinent of urine and fæces but there was no convulsion. After about half an hour he recovered consciousness but the attack was followed by an increase in the weakness and a considerable loss of sensation in the legs. The thermal loss was so marked that he sustained extensive burns as the result of sitting too close to the fire. Examination in the November, 1928, revealed a pale-faced, well-nourished man closely resembling his cousin, W. J. D. (No. 4) in his staring and vacant appearance. There was marked over-action of the facial muscles and his speech was explosive, jerky and very difficult to understand. He was emotionally unstable and had some difficulty in controlling his laughter. The discs were normal. The pupils were small and reacted to light, but no convergence or reaction on accommodation was obtained. The ocular movements into the outer canthi were deficient and accompanied by nystagmoid jerkings. No upward movement of the eyes was possible. Well-marked bilateral lid retraction with exophthalmos was observed. No strabismus or diplopia were present. The other cranial nerves were normal. Power was diminished in the arms, especially proximally: tone was normal. The left arm was somewhat inco-ordinate but there was no intention tremor. Strength in the lower extremities was fair; (the right leg was smaller than the left, the result of an old injury). There was no gross impairment of tone or of co-ordination. Some diminution of sensibility was evident in the legs, especially on the right side. Vibratory sense was absent at the malleoli. The knee and and ankle jerks were absent and there were bilateral Babinski responses. A peculiar feature lay in the fact that despite the apparent integrity of tone, power and co-ordination in the legs, this patient—like case No. 4—could not walk without assistance.

No. 20.—R. B. (*née* P.) born 1875. This patient was well until the age of 37, when she developed diplopia, which lasted fifteen months. At the same time she complained of unsteadiness of the legs, tremor of the hands and precipitancy with occasional incontinence of urine. The following year she became subject to vertiginous attacks and six months later the left eye turned in. When examined by Dr. Collier in 1913 the following physical signs were found; nystagmus on lateral ocular deviation, slight weakness of the left sixth and seventh nerves; slight hemiparesis; pallor of the right disc. There was some intention tremor of the arms; the legs were spastic and somewhat weak; tendon-jerks brisk; abdominal responses absent; bilateral extensor reflexes. Postural sensibility was defective in the legs: gait was spasto-ataxic. At the age of 45, she was admitted to King's College Hospital under the care of Sir David Ferrier. At that time her gait was much worse, the physical signs were the same as in 1913 with the exception that the ankle jerks were now absent. The diagnosis of cerebello-pontine tumour was made; the Wassermann reaction was negative in the blood. She was re-admitted the following year under the care of Dr. Aldren Turner because of difficulty in micturition. It was now noted that the articulation was not clear; there was some difficulty in swallowing and the tongue was tremulous. Examination of the cerebrospinal fluid gave normal results. The diagnosis was now changed to disseminated sclerosis. The same diagnosis was made at the Middlesex Hospital, where she was an in-patient in 1926, i.e., at the age of 51. When we examined her in 1928, her chief complaint was an inability to walk. There was no obvious psychical defect. Speech was extremely dysarthric. There was no diplopia but vision was misty in the left eye. There was a gross internal strabismus of the left eye and she had a habit of screwing up the left eyelid. The right eyelid showed at one time ptosis, at another lid retraction; there was a complete paralysis of the left abducens with weakness of the right; upward deviation of the eyes was impossible; there was no nystagmus. The left optic disc was pale, especially on the temporal side; the pupils reacted normally to light but less well on accommodation. Movement of the right face was better than of the left, and clonic twitchings were observable around the mouth. The fingers of the outstretched arms were in an attitude of over-extension and displayed pseudo-athetotic movements. Motor power was fair; co-ordination was poor especially on the right side but there was no intention tremor. Both legs were weak, especially the right. Tone was increased proximally, but diminished distally. The right knee-jerk was brisker than the left; the ankle-jerks were absent and there were no plantar responses. She was unable to stand without support. Some degree of scoliosis was observable.

No. 21.—T. P., male, born 1876. No details are known about this man except that he served in the Canadian Forces during the War. He died as the result of pneumonia and chronic alcoholism about 1918.

No. 22.—W. P., male, born 1878. When interviewed in 1929 it appeared that he was suffering from no neurological symptoms. He did not agree with the investigation and refused to be examined.

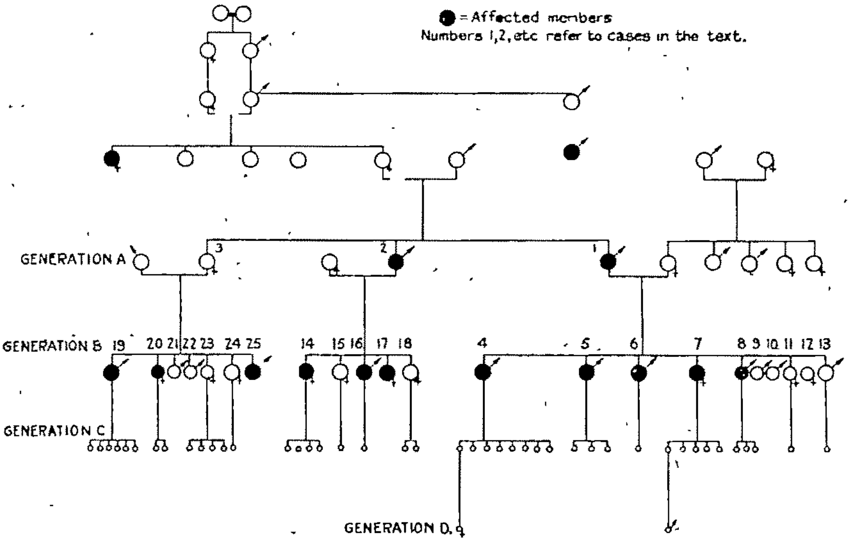
No. 23.—S. P., female, born 1880. As far as we know this person is living and unaffected, but we have not had the opportunity of examining her.

No. 24.—D. G. (*née* (D. P.), female, born 1882. This woman is living in Ireland and we have been unable to interview her. Her relations believe her to be alive and well.

No. 25 —C. S. P., male, born 1884. This man was quite well until the age of 33 when, while serving in France in 1916, he sustained a severe injury to the left knee. Since that time his legs have become increasingly weak; he found difficulty in getting about and could not resume work after demobilization. For the past two years he has complained of shooting pains in the left leg. In 1920 he attended the out-patient department at the West End Hospital (Dr. Worster-Drought), where he was treated for tabo-paresis. At that time the pupils were unequal; they reacted on accommodation but not to light. Ankle-jerks were absent and the plantar responses were flexor. The Wassermann reaction was strongly positive in the blood. The cerebrospinal fluid contained 42·7 cells per c.mm. (small lymphocytes with an occasional endothelial cell); albumen 0·03 per cent., globulin increased; Wassermann positive He remained under observation for two years and then ceased to attend the hospital. Examination in December 1928, revealed a middle-aged man with a strong facial resemblance to other members of the family, particularly to Case No. 7. The expression was rather blank and staring and there was bilateral lid retraction. His speech was a little unsteady, lalling and childish, he spoke explosively with forced expiration. There was some degree of euphoria but no marked mental change. The pupils were unequal and Argyll-Robertson in reaction, heterochromia-iridum was apparent. Eye movements were full except for a slight defect in lateral deviation. A fine tremor was noticeable in the face and tongue. Tone and strength were normal in the arms; co-ordination tests were jerkily performed and there was a fine intention tremor on the right side. Motor power was diminished in the legs, which were hypotonic. The feet were in an attitude of pes cavus with hyperextension of the great toes. There was marked dysmetria in performing the heel-knee tests. Areas of hypalgesia were demonstrable across the middle third of the face, the post-axial borders of the forearms, the chest and the legs. Vibratory sense was absent at the ankles and postural sensibility was defective in the fingers and toes. The arm-jerks were brisk, while the knee- and ankle-jerks were absent. Abdominal responses were obtainable; both plantar reflexes were extensor in type. He walked on a broad base with marked ataxia.

In *Generation C* there are forty-three members, seven of whom we have had the opportunity of examining. Nystagmus on lateral deviation was observed in three of these individuals, namely, the son of Mrs. C. P. (No. 7) aged 16, and the son and daughter of W. J. D. (No. 4) aged 18 and 13 respectively. The two male members who showed nystagmus had hypermetropic astigmatism. The eldest daughter of W. D., aged 20, had a sluggish ankle-jerk on the right side Complete neurological examination with especial reference to the relative features revealed no abnormalities other than those mentioned.

There are two children in *Generation D*, one of whom was examined. This child, the grand-daughter of C. P. (No. 7) showed slight defect in the upward deviation of the eyes; otherwise no abnormality was detected.



Clinical Manifestations.

In reviewing the clinical manifestations of the affected members of this family many points in the symptomatology demand more detailed consideration.

Age of onset.—The age of onset of ten of the thirteen affected members lay between 36 and 45; in the case of the other three the first symptoms appeared earlier, namely at 33, 27 and 21 respectively.

Sex.—The affected members included four females and nine males.

Course of the disease.—In every case in which we have details of the march of the disease the first symptom was found to consist in weakness and unsteadiness of the legs. This symptom was accompanied

—more frequently followed—by difficulty in speech, visual disturbances, dysæsthesiæ of the arms and legs, and bladder disorders. In two cases dysphagia was a troublesome complaint. Pain in the legs or back was present in three cases.

A study of the symptomatology of the patients reveals a striking similarity in the nature of complaints and in the order of their appearances.

The disease advances on the whole steadily; in no case could we discover any degree of improvement which we could consider a remission. In three instances a severe injury—necessitating confinement to bed—either immediately antedated or else aggravated the symptoms. The patient (R. B.) had numerous attacks of vertigo throughout her illness, each one of which was followed by an exacerbation in the symptoms. Another (H. P.) gave a history of an apoplectiform seizure which was followed by a marked deterioration in his physical condition.

The duration of the disease in the fatal cases was five years in two instances, and seven and ten in two others; in a fifth, death occurred from intercurrent disease at the end of one year. Of those that are still living, symptoms have been in existence in one case up to the extent of sixteen years, and in four other cases up to ten years or more. There appears to be no obvious association between the age of onset and the duration or severity of the symptoms.

SYMPTOMATOLOGY.

Psychical state.—The characteristic psychical picture comprises definite alterations in the emotional sphere. These take the form of a marked euphoria; there seems to be some definite instability in the prevailing mood and periods of depression and irritability were noted. A marked facility in emotional expression was very obvious, amounting at times to definite pathological laughter. In one case only (No. 6) was the prevailing mood one of depression; this patient had recently lost his wife. Intellectual deterioration was not a feature of these cases and in one case alone was the cerebration remarked upon as being abnormally retarded.

Ocular signs.—Alterations in the domain of the visual apparatus are important. In nine cases definite information is available as to the discs, pupils and eye movements.

In four cases there were definite signs of optic atrophy, characterized by a pallor of the temporal halves of the optic discs. Visual acuity was normal in those cases tested.

Pupillary reactions were normal in all except three; of these one had definite Argyll-Robertson pupils with anisocoria (this patient had a positive Wassermann reaction in the blood); in the other cases the pupils reacted to light but not on accommodation. In these two patients no convergence was obtained.

A marked feature in seven out of the nine cases examined was a defect or absence of upward movement of the eyes. Associated with this in six cases was a defect of lateral deviation, but the paralysis of upward movement was a much more striking feature. Diplopia was complained of by each of these seven patients. Strabismus was noted in one patient only (No. 20), in whom a complete paralysis of the abducens was present on one side. Nystagmus was present in eight of the nine cases.

A constant degree of lid retraction was noticeable in three of the patients; in two others the amount of retraction varied and at times there was some degree of ptosis.

Pyramidal signs.—Evidences of pyramidal disease were present in the majority of cases; thus in five out of the thirteen cases, some defect of motor power was noted in the arms; in nine patients weakness of the legs was observed. In four instances a definite degree of hypertonus was demonstrable in the legs. The distribution of this rigidity was peculiar in that the tone seemed to be increased in the proximal segments only, whilst the distal portion of the limb was hypotonic. A history of involuntary flexion spasms was given by three patients in our series.

Information as to the state of the reflexes is available in eight cases; the arm-jerks are reported as being brisk in four, normal in two, and absent or diminished in the other two. Interesting alterations occurred in the tendon-jerks of the legs. Absence of both knee and ankle jerks was found in two cases; in one of these, inactive pupils and a positive Wassermann reaction betrayed a co-existent tabes. In two other cases the knee-jerks were brisk while the ankle-jerks were absent; in the other two cases both knee and ankle jerks were brisk. Absence of the abdominal responses was found in only two patients; in six cases they were present, associated in three cases with bilateral Babinski responses. The plantar responses were of the extensor variety in five cases; in two patients no response could be obtained. Another patient gave a flexor response on one side and none on the other. One patient only showed a bilateral flexor reflex.

Cerebellar signs.—A cerebellar type of inco-ordination was noted in several of our patients; thus in three cases there was an intention tremor in the arms, whilst dyssynergia and hypermetria were noted in the upper extremities in three other cases; in five patients co-ordination was found to be normal. Inco-ordination of the legs was present in three cases in one of which there was intention tremor.

Speech defect was noted in no less than twelve cases; as will be discussed later, the nature of this defect is complicated. In many of the cases a definite cerebellar component was betrayed by a scanning or staccato element, and was combined with some degree of nasal intonation. Nystagmus has already been referred to as occurring in eight out of nine cases; in each instance the movement was evoked by lateral deviation of the eyes. The nystagmus was rhythmic, horizontal in direction and well sustained.

Extra-pyramidal signs.—A striking feature of many of our patients was found in a peculiar facial appearance. In a number of cases there was a definite blankness or fixity of expression, amounting at times to a true Parkinsonian mask. Some degree of facial immobility was noted in six out of nine of our patients. Other features recalling Parkinsonism were the striking poverty of movement in many of our patients, which was often coupled with an attitude of flexion and a distinct slowness of movement. Tremor was a conspicuous feature in several cases; in seven, facial tremor, varying from abrupt shock-like twitchings to a constant and rhythmic flickering of the muscles around the mouth was seen. In many there was a striking resemblance to the typical facial tremor of Parkinsonism. Tremor of the tongue was present in three. In five cases tremor occurred in the hands; in two of these it was very fine and rapid and only appeared when the arms were outstretched, but in one or two of the others (particularly Case 1) the tremor was slower and coarser and was visible when the hands were at rest, and bore an obvious resemblance to the pill-rolling tremor of paralysis agitans. A typical Parkinsonian tremor was visible in the legs in two cases.

Associated with the cerebellar component of the dysarthria, features of an extra-pyramidal type were often noticeable. The monotonous and dysarthric characters recalled those seen in Parkinsonian states.

Sensory disturbances.—Diminution to light touch and pin-prick was noted in eight cases; as a rule this amounted to an impairment only and it was most marked in the legs. Occasionally it was also found over the lower part of the trunk. Although usually symmetrical in appearance, in one instance sensory impairment affected one side only.

Defects in postural and vibratory sensibility were less common, being present in six cases only. In two instances these forms of sensation were intact, although there were widespread areas of hypæsthesiæ. It must be remembered that Case 5, included in the above, showed signs of a co-existent tabes. Rombergism was present in six cases—that is to say in every one who could stand unaided.

Gait.—Defects of gait occurred in every case, varying from a slight unsteadiness or stiffness of the legs to the most extreme degree of spastic-ataxia. In the final stages the patient was quite unable to stand. Defects of a pyramidal, extra-pyramidal, sensory and cerebellar order are demonstrable in the disturbance of gait.

Speech.—In every patient some disorder of speech was noted ; in the early stages the defect may be so slight as to escape casual detection, while when the disease is well established a dysarthria may render the patient almost unintelligible. Typically, the speech is lalling, monotonous and stacatto ; articulation is obviously defective ; the accompanying respiratory movements may be inco-ordinate, imparting an explosive quality to the speech. The rate of talking, which is possibly somewhat accelerated in the early stages, later becomes distinctly slow.

Sphincters.—Some disturbance of sphincter control was exhibited by six of the nine patients of whom we have a more detailed account. The most common abnormality was frequency and precipitancy of micturition leading to occasional incontinence. In one case only was the complaint that of hesitancy.

Bony deformities.—It is striking that in only two cases have we any note as to the existence of pes cavus, in view of the frequency of this symptom in other heredo-familial ataxies. Similarly spinal curvature of lordotic nature was noted in two cases alone.

It is obvious from this consideration of the clinical manifestations that certain features were present in most of the affected members. The common features are :—

(1) Age of onset of symptoms at 35-45.

(2) Similarity in the nature and order of appearance of the symptoms.

(3) Absence of remissions in the course of the disease.

(4) Euphoria and emotional instability.

(5) Ocular pareses, nystagmus and (at times) optic atrophy.

(6) Evidence of pyramidal disease.

(7) Widespread sensory disturbance.

(8) Certain extrapyramidal manifestations.

(9) Articulatory defects.
(10) Disturbance of sphincter control.

DISCUSSION.

The question arises at this stage as to which category of familial diseases this family belongs. At least two members were regarded at one period as suffering from disseminated sclerosis and it was not until a fuller investigation of the family was made that this diagnosis was doubted. Nevertheless the possibility presented itself that this syndrome was one of familial disseminated sclerosis, and indeed one case was discharged after several months' observation at the National Hospital as "indistinguishable from disseminated sclerosis." Examination of individual members with spastic paraplegia, cerebellar and sensory changes, optic atrophy, and a peculiar temperamental state with euphoria, at first strongly supports this contention. Further investigation reveals many points which are incompatible with this diagnosis, as for example, the absence of exacerbations and remissions, the lack of history of retrobulbar neuritis, the presence of well-marked ocular palsies and the absence of ankle-jerks. Further, Parkinsonian signs were in some cases so striking as to dominate the picture; thus Case 1 left the National Hospital where he had been treated for four months by Sir William Gowers, with the tentative diagnosis of paralysis agitans. A survey of this family shows at one end of the scale cases which are almost indistinguishable from Parkinson's disease, and at the other cases simulating disseminated sclerosis; while other members of the family show various combinations of the features belonging to these two diseases.

The large number of individuals affected in this family is remarkable and contrasts strongly with the reported instances of familial disseminated sclerosis where two or at the most three members are afflicted.

There are a number of recorded cases of disseminated sclerosis occurring in families and every neurologist has probably met with three or four such instances. Certain of the recorded examples will not bear scrutiny and in the light of further knowledge have proved to belong to some other clinical category; thus, the cases of Pelizæus and Merzbacher almost certainly belong to the group of Schilder's disease; Pesker's cases were obviously not examples of disseminated sclerosis. Despite the comparative frequency of clinical evidences of genuine cases of familial disseminated sclerosis, the lack of pathological verification is striking. In fact, this has been recorded in two instances only, namely, those of Eichhorst and of Leuch, and in both doubt has been cast on the anatomical diagnoses by Müller.

Peculiar importance can be attached to this present family, for had two members only come under observation no hesitation would have arisen in regarding them as cases of familial disseminated sclerosis. It is possible that with more intimate knowledge of the pedigree other of the recorded instances will prove to belong to other varieties of familial disease.

In view of the manifestations referable to the basal ganglia in our cases, differentiation has to be made from the familial extrapyramidal disorders. The diagnosis of progressive lenticular degeneration hardly enters into the problem, but the relationship with "pseudo-sclerosis" will require discussion. Although very rarely diagnosed in this country, the title pseudo-sclerosis is often applied on the Continent to familial diseases in which extrapyramidal motor disturbances are prominent. The earlier cases of Westphal, Strümpell and others bore but little resemblance one to another, and probably represented a heterogeneous collection of obscure syndromes, but nevertheless the term pseudo-sclerosis has since 1912 been more restricted and is now made to apply more narrowly to a well-defined clinical picture. The relationship of this disease to progressive lenticular degeneration and the existence of transitional types need not be discussed here. It is clear, however, that at one end of the scale of hepato-lenticular disorders is a distinct symptom-complex to which the label pseudo-sclerosis is applicable. Such cases are characterized by an onset in adult life (thirty to forty-five), a slowly progressive course in which muscular rigidity, mask-like features, slight speech defect, dysphagia, mental and emotional changes are conspicuous. A Kayser-Fleischer zone of corneal pigmentation has been observed in a number of instances.

Our cases recall those of pseudo-sclerosis in exemplifying a familial affection of the motor system with numerous extra-pyramidal features; the fact that our cases occur in at least two generations does not exclude the diagnosis of pseudo-sclerosis. Nor does the presence of pyramidal signs which have been noted by several observers (Hall [11] and others). While nystagmus has been seen in one case of pseudo-sclerosis (Fleischer [10]) and strabismus has also been noted once, in the great majority of instances of this condition there is no defect of the ocular movements. Optic atrophy, of course, forms no part of the clinical picture of pseudo-sclerosis. These points, together with the presence of sensory and cerebellar signs, argue strongly against the conception of our cases as examples of pseudo-sclerosis.

In view of the fact that at least three members of this family had a positive Wassermann reaction in the blood (Nos. 5, 6, and 25), it is necessary to consider heredo-familial neuro-syphilis as a diagnostic possibility. The demonstration of physical signs suggestive of tabes in two instances (Nos. 5 and 25) may be mentioned. It must be admitted, however, that the clinical appearances of this particular affection are quite unlike any of the usual manifestations of congenital syphilis of the nervous system. This point, quite apart from the lack of serological evidence in many cases, justifies the conclusion that the occurrence of syphilis is merely incidental and plays no essential part in pathogenesis.

Among the familial disorders confined to the cerebellum, Holmes' family [13] is the one which approximates most closely to our cases. Three brothers and a sister were affected with a slowly progressive incoordination, commencing in the legs, spreading to the arms and lastly involving the speech mechanism and the facial muscles. The age of onset was between 35 and 38. Examination revealed cerebellar incoordination of arms and legs, nystagmoid jerkings of the eyes, dysarthria and tremor of the head and extremities. There was no disorder of sensation and sphincter control was normal. The knee-jerks were brisk and there was no clonus. Optic atrophy did not occur. Our cases are distinguishable by the presence of ocular defects, as well as sensory and pyramidal signs. Lastly, Holmes patients were all undersized individuals with infantile genitalia and very scanty hirsuties.

The possible relationship of this family to the better-known examples of the familial ataxies may be considered. Because of the late age of onset and the course of the affection, our cases are unlike the usual picture of Friedreich's ataxia, but the question of the relationship to the heredo-cerebellar ataxia of Marie and Londe requires investigation.

More recently it has become customary to take a broad conception of Marie's ataxia, and by expanding the symptomatological confines of the disease to make room for various atypical and rarer cases of heredo-familial ataxia. The chaotic state of our knowledge of the familial cerebellar disorders is due in large part to the absence of morbid anatomical data in the great majority of reported instances. Two possible points of view may be taken, therefore, with regard to the family diseases; disregarding the pathological aspect of the problem, which is sadly incomplete, we may regard them all as examples of a very elastic nosological group, namely, Marie's ataxia; on the other hand, in view of the possibly distinct pathological basis to each form, we may restrict the term Marie's ataxia to those cases which conform strictly to the clinical description given by Marie [18]. The numerous anomalous forms which belong to no definite clinical group and in which the pathology is unknown or not characteristic are then regarded as distinct self-contained entities, which may or may not justify their title as clinico-pathological entities in the light of future knowledge.

The insecurity of the claims of Marie's disease as a distinct nosological entity with a characteristic pathological picture, has been emphasized by Holmes. By pointing out the lack of evidence of cerebellar disease in cases which were relegated by Marie himself into the group of "hérédo-ataxie cérébelleuse," Holmes [12] has thrown doubt not only on the anatomical basis of the syndrome, but also on its claim to uniformity of clinical features. "We are consequently driven to the conclusion," he writes, "that no form of disease exists to which the term 'hereditary cerebellar ataxy' can be aptly applied. This title has been a convenient pigeon-hole in which to group together cases of obscure nature with some symptoms in common, and it may have been of some service in drawing attention to such cases until it was possible to classify them accurately; but neither clinical nor pathological experience justifies its retention as the descriptive title of a form of disease."

If we take a narrow conception of Marie's ataxia as an entity characterized by combined pyramido-cerebellar signs appearing in adolescence and often accompanied by optic atrophy, points of distinction from our family will be found. Thus our cases show in many instances signs of sensory and extrapyramidal motor disturbance which form no part of the semiology of Marie's ataxia. Again, the later age of onset and the frequent absence of the ankle-jerk are points of differentiation.

If, however, the broader conception of Marie's ataxia be adopted, then it will be necessary to compare this present family with the cases recorded by Neff, Sanger Brown, Klippel and Durante, Dobrochotow, by Ballet and Rose and by Batten and others.

In some respects these cases resemble the family reported by Sanger Brown [4]. The age of onset, the ocular palsies, the absence of scoliosis, the presence of optic atrophy, the large number of members affected are points of similarity in the two families. On the other hand, there was no nystagmus, no sensory loss, little or no evidence of involvement of the pyramidal tracts and no extrapyramidal signs in Sanger Brown's cases.

The family described by Klippel and Durante [14] (subsequently expanded by Londe [16] and Vincelet [25]) deserves special attention. Although included by Marie when he made his original category of hereditary cerebellar ataxia, there are certain clinical features foreign to the usually accepted conception of Marie's disease, and the cerebellum was healthy. The Klippel-Durante family comprised three members who were personally examined; two members of the previous generation were said also to have been similarly affected. The onset occurred between the ages of 25 and 35. The outstanding clinical features were immobility of the face, dysarthria, nystagmoid jerkings of the eyes, fibrillation of the limbs and face and frequent intermittent muscle cramps. There was a generalized rigidity and slowness of movement, with some impairment of motor power; true ataxia was not present. Impaired sensibility to painful and thermal stimuli was present over the legs and feet. The knee-jerks were exaggerated, but in one case they were subsequently lost. The plantar responses were extensor in type in the only case in which this point was noted.

Neff's family [20] is striking in that thirteen members belonging to four generations were affected. The symptoms consisted in weakness and unsteadiness of legs, later affecting the arms; later still the speech became disordered and dimness of vision and diplopia appeared. Incoordination of legs and arms were revealed on examination; tremor of face, tongue and body were visible and were increased on volitional activity. The speech was tremulous, explosive and dysarthric; indefinite sensory impairment was present below the knees; the tendon-jerks were exaggerated, but the superficial reflexes were normal. A slight degree of optic atrophy was described, but there was no defect in the pupils or in ocular movements. Four of the thirteen patients became demented. Neff's cases differed from ours in the later age of onset of symptoms; eleven of Neff's patients were affected between the ages of 50 and 65, and in two others the age of onset was 72 and 68 respectively.

Miura's cases [19] are worthy of note in that immobility of the face recalls the cases in our family. Two brothers were affected, though probably the mother and two maternal cousins were also similarly afflicted. Symptoms commenced at 25 in one and 33 in the other. The chief clinical manifestations were reeling gait, dysarthric explosive speech, nystagmus (in one case) and dimness of vision. The limbs were tremulous, ataxic and poor in strength. No sensory or reflex changes were noted. Neither were there any abnormalities in the range of eye movement, which were present in our cases.

In 1900, Cestan and Guillain [5] reported two families exhibiting unusual signs; the second family bore some resemblance to the cases in our series. "Famille B" comprised ten siblings, two of whom were epileptics. Two others had signs of a neuro-muscular disorder dating from childhood. In the case of the elder, a defect in gait had been noted since the age of 5; at 22 the speech became affected. At this time she was taken to Charcot who diagnosed disseminated sclerosis. When examined at the age of 31 she was found to have spastic legs with signs of pyramidal affection and deformity of the feet, an intention tremor was present in the arms and there was nystagmus on lateral ocular deviation. The speech was slow and scanning. Her brother, aged 16, had been awkward on his legs since earliest infancy. Dysarthria had been noticed first when he was fifteen. He was obviously of inferior mental development; his neurological signs resembled those in his sister except that there was a very marked element of cerebellar inco-ordination in his gait. Cestan and Guillain regarded these cases as examples of a "maladie familiale à forme clinique de sclérose en plaques." The patients in our series are differentiated by the presence of other manifestations, particularly the ocular, sensory and extrapyramidal signs and the existence of bladder disturbances.

The family described by Ballet and Rose [2] comprised a brother and two sisters who first showed symptoms in early adult life. Spastic paraplegia with pyramidal manifestations, spasticity of the face, defective eye movements, disorders of speech and mental change made up the clinical picture. Here again there are points of distinction from our cases; the absence of sensory, cerebellar and extrapyramidal signs, and the increased ankle-jerks separating the cases of Ballet and Rose.

Batten's cases [1] are of especial interest in that they were regarded in some quarters as instances of familial disseminated sclerosis. They comprised a sister and a brother. The former, aged 27, had suffered for two years from tremor of the hands which was accentuated when she attempted to grasp anything. Four months later the legs became weak, she became unsteady in walking and the speech grew thick. Nystagmus was not present and there was no optic atrophy. There was an intention tremor in both arms; both legs were ataxic but there was no sign of spasticity in the limbs. Her brother, aged 25, had been afflicted for four years with pains in the legs and unsteadiness of the gait. The physical signs closely resembled those in the sister with the additional feature that diplopia was here present.

The combination of absence of the ankle-jerks with lively knee-jerks and extensor plantar responses recalls the syndrome recorded by Purves Stewart [23] under the title of "Familial Amaurotic Ataxic Paraplegia." His patients—two brothers and a sister—suffered from optic atrophy, strabismus, cerebellar ataxia and disordered gait. Signs of pyramidal affection were also present. Stewart's cases differed from our present family in the presence of intense visual defect, present in two instances since birth.

Dobrochotow [7] reported a form of familial disease occurring in eleven members in two generations. The symptoms comprised a spastic paraplegia of pyramidal type, combined with nystagmus, scanning speech and dysphagia. The symptoms appeared in childhood at the time of the second dentition. The early onset and the absence of ataxia, sensory and extrapyramidal changes are points of dissent from our cases.

In certain respects our cases are comparable with the remarkable family recorded by Crouzon and Bouttier [6]. The clinical features in both comprise speech defects, a fixed "spastic" facies, and flail-like ankle-joints with absence of the ankle-jerks. Definite evidences of muscular atrophy, with no ocular paralyses or sensory loss, distinguish the Crouzon-Bouttier syndrome.

Again one may compare the symptoms of this present family with those occurring in the peculiar transition types between Friedreich's ataxia and hereditary cerebellar ataxia, described by Perrero [21], Margulies [17], Lenoble [15], by Menzel, Gotthard, and by Söderbergh [22]. The instances quoted by Bayer and Gy [3], Ferrier and Chassin [9], may be mentioned in which Friedreich's and Marie's ataxia occurred in different members of the same family.

Despite the numerous aberrant types of heredo-familial ataxia which have been recorded as isolated examples in the literature we have been unable to find any case or case-group which corresponds to any extent with our family. In the absence of pathological data it is, of course, impossible to place our cases into a definite category, but as a provisional step we must consider whether or not to relegate them to the pigeon-hole of Marie's ataxia. If we are content to adopt a catholic view of this syndrome then there is no doubt that our cases can well be included here. But if we restrict Marie's ataxia to its narrower sense, then it is obvious that our cases form an entity which is very far removed.

There are three diagnostic possibilities with regard to our family. First, we may describe our cases as examples of a new familial disorder. Secondly, we may regard our family as an atypical example of some already described ataxia, as, for example, Marie's ataxia. Lastly, we may associate ourselves with Raymond's unitary conception of the heredo-familial ataxias, and group together the disorders described by Friedreich, Marie, Sanger Brown and others.

But the classification of the heredo-familial ataxias is undoubtedly most unsatisfactory for several reasons. In the first place, many dissimilar cases have been relegated to artificial categories, as Holmes has shown in the case of Marie's ataxia. Secondly, many of the better known nosological types remain confined to the family originally recorded; e.g., the cases of Sanger Brown, of Neff, Crouzon and Bouttier. In the third place, the present artificial mode of classification either ignores the incomplete forms or else places them as separate entities. Thus we see that with our present knowledge the differentiation of these heredo-familial ataxias into "types" and the employment of a nomenclature based on an individual author's name is to be deprecated as being misleading.

These difficulties have arisen chiefly because hitherto an almost exclusively anatomical classification based upon the particular system or systems affected has been adopted. The fallacy of this is illustrated by the occurrence of both Friedreich's and Marie's ataxy within the same family; such an incidence within a single family suggests a similar pathological process differing only in anatomical distribution.

The Drew family illustrates the same point. Presumably the pathological process is here identical in all the affected members; yet clinically the cases varied markedly because of the varied anatomical incidence of the process. We have seen that in our family almost any system within the brain and spinal cord may be involved, pyramidal, extra-pyramidal, sensory or cerebellar. Yet the degree to which they were involved was so variable, and the resulting clinical aspect so different, that individual members resembled such widely divergent diseases as paralysis agitans and disseminated sclerosis. Had the number of affected members not been so large, and had we not been offered such an unique opportunity for comparative study we might have been tempted to regard two or three of them as cases of an "heredo-familial disease resembling Parkinsonism" (cf. Bechet), and others as instances of an "heredo-familial disease resembling disseminated sclerosis." Thus our cases are of value because they illustrate how in one family different clinical pictures, resembling almost any known type of heredo-familial ataxia, may result from a variation in the relative affection of the different systems, all of which were affected in most cases to some degree.

In the absence of pathological evidence—both in our cases and in those recorded in the literature—we are unable to confirm our suggestion as to the possible unity of the heredo-familial ataxias, but we are probably justified in regarding them all as abiotrophies differing merely in anatomical incidence or in viability.

BIBLIOGRAPHY.

[1] Batten, F. E. "Two Cases of a Family Disease, the Symptoms of which closely resemble Disseminated Sclerosis," *Proc. Roy. Soc. Med.* (Neurol. Sect), 1908-09, **2**, 35.

[2] Ballet, G., and Rose, F. "Affection bulbo-spinale spasmodique familiale," *Rev. Neurol* , 1905, **13**, 353.

[3] Bayer and Gy. "Maladie de Friedreich et hérédo-ataxie cérébelleuse dans une même famille ; maladie de Friedreich avec lymphocytose rachidienne," *ibid* , 1909, **17**, 97.

[4] Brown, Sanger. "On Hereditary Ataxia, with a Series of Twenty-one Cases," *Brain*, 1892, **15**, 250.

[5] Cestan and Guillain, G. "La paraplégie spasmodique familiale et la sclérose en plaques familiales," *Rev. de Méd.*, 1900, **20**, 813.

[6] Crouzon and Bouttier "Sur une variété singulière d'amyotrophie familiale," *Bull. et Mém. Soc. des Hôp. de Paris*, 1919, **43** (3me série), 1097.

[7] Dobrochotow. "Ein Fall von hereditärer Familienerkrankung vom Uebergangstypus zwischen spastischer Spinalparalyse und Friedreichscher Krankheit," *Deutsch. Zeitschr. f. Nervenheilk.*, 1913-14, **49**, 1.

[8] Ferguson, Fergus R. "Familial Ataxia resembling Disseminated Sclerosis," *Proc. Roy. Soc. Med.* (Neurol. Sect.), 1928, **22**, 9.

[9] Ferrier and Chassin. "Cas atypique de maladie de Friedreich," *Bull. et Mém. Soc. des Hôp. de Paris*, 1906, **35**, 23, 880.

[10] Fleischer. "Ueber eine der 'Pseudosclerose' nahestende bisher umbekannte Krankheit, gekennzeichnet durch Tremor, psychische Storungen, braunliche Pigmentierung bestimmter Gewebe, inbesondere auch der Hornhautperipherie, Lebercirrhose," *Deutsch. Zeitschr. f. Nervenheilk.*, 1912, **44**, 179.

[11] Hall, H. C. "La dégénerescence hépato-lenticulaire," Masson et Cie, Paris, 1921.

[12] Holmes, G. "An Attempt to Classify Cerebellar Disease, with a Note on Marie's Hereditary Cerebellar Ataxia," *Brain*, 1907, **30**, 545.

[13] *Idem.* "A Form of Familial Degeneration of the Cerebellum," *ibid* , 1907, **30**, 466.

[14] Klippel and Durante. "Contribution à l'étude des affections nerveuses familiales et héréditaires," *Rev. de Méd.*, 1892, **12**, 745.

[15] Lenoble, E., and Aubineau, E. "Deux cas de maladie nerveuse familiale inter. médiare entre la maladie de P. Marie (hérédo-ataxie cérébelleuse) et la maladie de Freidreich," *Rev. Neurol.*, 1901, **9**, 893.

[16] Londe. "Hérédo-ataxie cérébelleuse," *Thèse de Paris*, 1895.

[17] Margulies, A. "Ein Beitrag zu den Uebergangsformen zwischen Friedreichscher Ataxie und der Hérédo-Ataxie Cérébelleuse von Marie," Berlin, 1901.

[18] Marie: P "Sur l'hérédo-ataxie cérébelleuse," *La Semaine Med.*, 1893, **13**, 444

[19] Miura, K. "Ueber l hérédo-ataxie cérébelleuse, Marie's,' " *Mitth. Med. Facult. Univ. Tokio*, 1900, **4**, 19.

[20] Neff, I. H. "A Report of Thirteen Cases of Ataxia in Adults with Hereditary History," *Amer. Journ. Insan.*, 1894-95, **51**, 365.

[21] Perrero, E. "Sopra le forme di transizione fra il morbo di Friedreich e l'eredo-atassia cerebellare di P. Marie," *Arch. di Psych.*, 1906, **27**, 565.

[22] Soderbergh, G. "Un cas de maladie familiale avec symptômes de maladie de Friedreich et l'hérédo-ataxie cérébelleuse très ameliorés par les rayons X," *Rev. Neurol.*, 1910, **18**, 7.

[23] Stewart, J. Purves. "Familial Amaurotic Ataxic Paraplegia," *Rev. Neurol. and Psychiat.*, 1912, **10**, 357.

[24] Vincelet. "Étude sur l'anatomie pathologique de la maladie de Friedreich," *Thèse de Paris*, 1900.

TUMOURS OF THE PINEAL, CORPORA QUADRIGEMINA AND THIRD VENTRICLE, THE INTER-RELATIONSHIP OF THEIR SYNDROMES AND THEIR SURGICAL TREATMENT.[1]

BY MARK ALBERT GLASER, M.D.
Philadelphia, Pennsylvania.

(*Read at the Los Angeles County Neurological Society, October* 2, 1928.)

NEOPLASMS involving the mid-central region of the brain may be considered as among the less frequently occurring brain tumours. In the majority of cases the diagnosis has been made post mortem, and even when a clinical diagnosis has been possible the condition has been regarded as not amenable to treatment. With increasing refinement of diagnostic methods and of surgical technique such a view is no longer justified, and for this reason it is proposed to dwell particularly upon the more accurate means of differential diagnosis and upon the newer surgical methods of approach.

A survey of the literature illustrates the vagueness of the clinical indications of tumour involving these regions and also the fact than in each case the clinical pictures may be similar. Although the structures involved are closely related anatomically, certain differential criteria occur with sufficient frequency to be of diagnostic value, as the study of cases recorded in the literature and of the twelve cases described in the present paper show.

TUMOURS OF THE PINEAL.

From time to time numerous observers have described the clinical signs of tumours of the pineal body (Frankl Hochwart, Marburg, Krabbe, Monchy, Pearce Bailey, Jelliffe, Horrax and Percival Bailey). They may be divided into those of neurological origin and those of endocrine disturbance. Experimental studies of the pineal have given rise to many contradictory opinions and have failed to assign decisively any definite function to it (Adler, Exner and Boese, Foa, Sarteschi, Berkeley, Goetsch, Dana, McCord, Dandy, Gudernatch, Tilney, Warren and Izawa).

---

[1] From the Neuro-Surgical Division of Charles H. Frazier, University of Pennsylvania, Philadelphia.

Clinically, from an endocrine standpoint there have been reported cases in the pre-adolescent age which presented the characteristic macrogenitosomia præcox. These, however, have been in the minority and on their neurological signs only could a definite diagnosis be made. This pre-adolescent syndrome includes such signs of enlargement of the body, deep voice, excessive growth, premature sexual development and mental precocity. No such symptoms have been produced by experimental procedures on the pineal gland. On the other hand, experimental work on the function of the anterior lobe of the hypophysis has indicated the existence of a hormone which produces a true overgrowth of the body, both skeletal and visceral, the reproductive tract, uterus and oviduct remaining infantile. However, microscopic examination of the ovaries demonstrated sexual maturity (Evans, Long and Smith). Polyuria has occurred in clinical cases of pineal tumour. Camus, Roussey, Bailey, Bremer and Souques, Baruk Bertrand and Fulton, have been slowly accumulating evidence indicating the existence of centres for the regulation of temperature, sleep and water and carbohydrate metabolism in the floor of the diencephalon. The earlier experimenters are still of the opinion that the pituitary has control over carbohydrate metabolism (Smith, etc.).

The neurological symptoms resulting from tumours of the pineal depend not upon any presumed function of the pineal body itself, but upon pressure or destruction of adjacent anatomical areas. These may be divided and classified into six respective groups, namely: (1) ocular; (2) cerebellar; (3) sensory; (4) motor; (5) other cranial nerves, and (6) the signs of increased intracranial pressure.

Involvement of the ocular apparatus causes the most outstanding diagnostic sign, which in Horrax's series was the loss of associated upward movement of both eyeballs. There occur also a failure of conjugate movement downward, rhythmic convergent spasm, as well as unequal immobile and widely dilated pupils, sluggish pupillary reaction to light, Argyll-Robertson's sign, paralysis of convergence, unilateral or bilateral sixth nerve paralysis, unilateral ptosis and diplopia.

Cerebellar symptoms have been described and manifest themselves in staggering gait, ataxia of the limbs, lateropulsion and retropulsion.

Sensory symptoms such as unilateral hypæsthesia have been observed, and motor tract signs are represented by bilateral or unilateral spasticity, facial paresis and the presence of pathological changes in the reflexes.

Other cranial nerves have been involved, such as the eighth, with unilateral or bilateral deafness of central origin, with buzzing, crackling and ringing in the ears. Fifth nerve anæsthesia had also been observed.

In the reported cases one finds the symptoms of increased intracranial pressure, such as headaches, nausea, vomiting, drowsiness, stupor, nose-rubbing and itching, choked disc, cracked-pot sound; and X-ray indications, as convolutional atrophy, widening of the sutures, erosion of the anterior and posterior clinoid processes and enlargement of the sella turcica. Case 1, herein presented, showed ocular abnormalities, such as widely dilated pupils and bilateral sixth nerve palsy, and increased intracranial pressure of one year's duration. Frequently in tumours of the pineal the intracranial hypertension is very rapid in onset and of high degree. Anatomically a tumour of the pineal growing in path of least resistance will quickly obstruct the aqueduct, thus accounting for the sudden onset of increased pressure.

Case 1 is a particularly good example of a pinealoma completely filling the third ventricle. It occurred in a child, aged six, without sexual precocity, but with signs of increased intracranial pressure, involvement of the ocular apparatus and signs of cerebellar disorder. However, in this case involvement of the ocular apparatus was shown by dilated pupils, not by the loss of associated upward movements of the eyes.

Case 1.—H.R., a child, aged 6, admitted to Neuro-Surgical Service, Univ. of Penn. Hosp., July 20, 1926. 9102.

Complaint.—Headaches, nausea and vomiting.

Family history.—Father died of heart disease; mother living and well; three brothers living and well.

Past history.—Normal delivery, normal development.

Present illness.—About a year ago she began to develop periodic attacks of frontal headaches lasting two to three days and occurring every month or so. Associated with these headaches there were nausea and vomiting The patient was very drowsy and did not play.

One month before entry she complained of diplopia, and soon afterwards her left eye turned inwards. A few days later her right eye also turned inwards. Photophobia then developed and she became very forgetful. One week before entry her memory became impaired, she was very fretful and her eyes took on a staring appearance.

General physical examination.—She was a well developed girl of 6 years. Flexion of the neck produced frontal headaches. There was slight enlargement of the anterior and posterior cervical glands, The chest and abdomen, as well as the genitalia and the extremities, were normal.

Neurological examination.—She had bilateral choked discs; the visual fields normal; pupils were widely dilated, equal, regular and reacted to light.

There was a bilateral sixth nerve paralysis. Remaining cranial nerves were normal. She was able to walk. No weakness of the arms or legs was observed and there were no sensory disturbances. Deep reflexes were not absent and there was no clonus; abdominal reflexes sluggish; no Babinski. The gait was somewhat ataxic, with Rombergism and a tendency to stagger to the right.

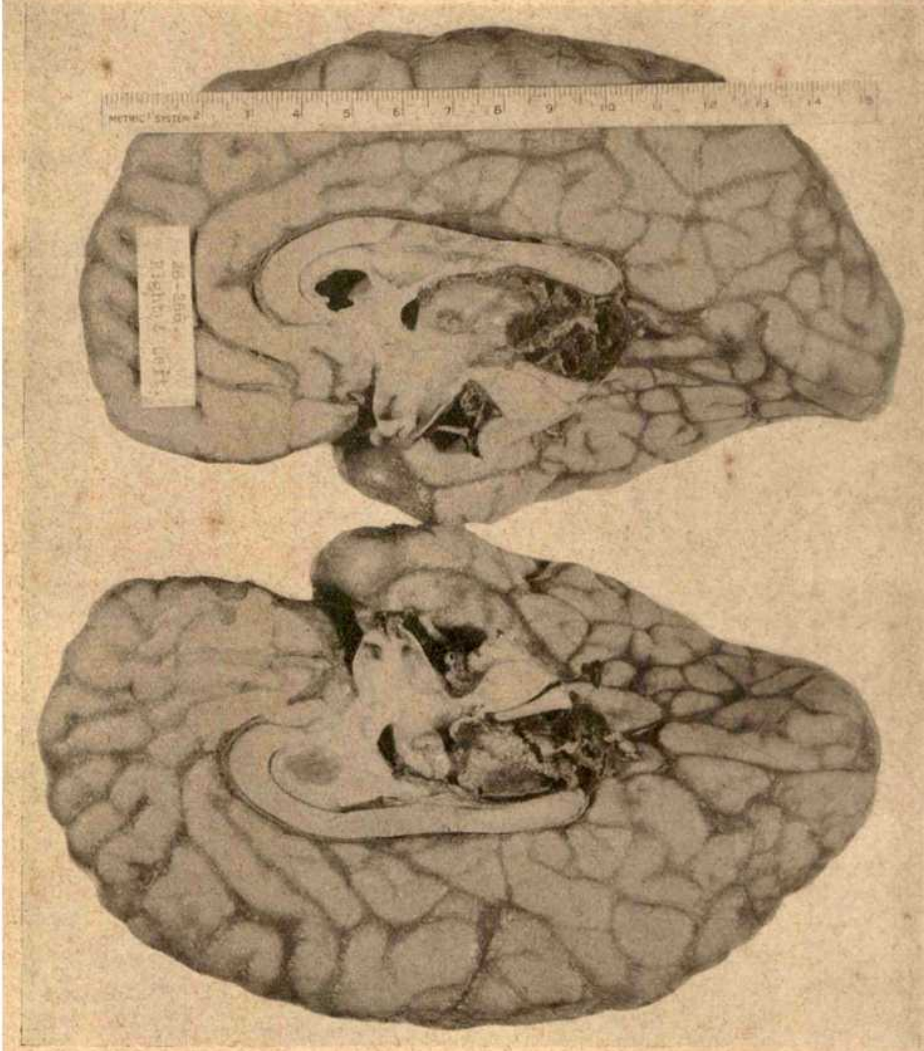


FIG. 1.—(Case 1.) Pinealoma distending the third ventricle.

Laboratory examination.—Complete blood and urine examinations were normal. Radiographs of head showed increased intracranial pressure with slight convolutional atrophy. No sellar changes were seen. Spinal puncture was not done. Vestibular test: past pointing after stimulation was markedly impaired; this suggested a cerebellar lesion. Vertigo responses, however, do not appear to be interfered with, which was against a cerebellar lesion, although the case looked like one of disease in the posterior fossa. Patient died while in hospital.

Necropsy.—The size of the brain was above the usual for a child of 6 years. The consistency was normal. There was no asymmetry. The pia arachnoid over the convex cerebral surface was faintly misty and slightly but definitely blood stained. This was most noticeable over the surface of the pons and over the lateral aspects of the brain. The pons was soft to the touch. The basal vessels were of normal size and did not present any peculiarity. The interpeduncular space bulged symmetrically. The bulging appeared under the optic chiasma and was of the size of a small marble. There was a slight amount of scattered dried clot over the upper portion of the dura close to the medial plane. When the dura was removed from the mesial fissure the pineal body was removed also. It was a spongy mass which ruptured and from it blood oozed. By the rupture caused by its removal an opening was made into the ventricle, from which bloody fluid oozed.

A vertical sagittal section was then made. This revealed a brownish mass, apparently an overgrowth of the pineal body, which extended into the ventricle and as far forward as the massa intermedia (fig. 1). It measured 3½ cm. in antero-posterior diameter, 2 cm. in transverse diameter and 1½ cm. in vertical direction. Thus it was evident that the third ventricle had been greatly distended. This mass conformed to and completely filled the dilated portion of the ventricle. Except where it was attached to the pineal body it could be lifted from its bed. The surface was quite smooth. The consistency of the neoplasm showed a fine grain, homogeneous in character, dark brown in colour, and was surrounded by what appeared to be a capsule of 1 mm. thickness. Section of the cerebellar hemispheres revealed no abnormality other than a thickening of the meninges as they clothed the pons. It was about ½ mm. in thickness.

Microscopical description.—The tumour possessed a very cellular structure and contained many thin-walled vessels about which the cells were sometimes arranged in the form of a perivascular rosette. The specimen contained but little connective tissue apart from that present in the vessels, and no islands of lymphoid cells such as are seen in the normal pineal body. The cells contained round or oval nuclei with abundant chromatin. The cytoplasm was scanty, indefinite or streamed away from the cell in the form of a tail.

Diagnosis.—Pinealoma extending into the third ventricle. Internal hydrocephalus. (N. W. Winkelman.)

CORPORA QUADRIGEMINA.

To the quadrigeminal plate itself there has been assigned a multiplicity of functions. The earlier writers were of the opinion that

isolated destruction of the anterior corpora quadrigemina resulted in blindness. Bach and Nissen definitely demonstrated that blindness in these cases was not due to quadrigeminal destruction, but depended upon the concurrent existence of increased intracranial pressure and choked discs. Hoppe, among the more recent writers, agreed with these observers. Cases 2 and 3 of this series would seem to verify these conclusions. However, if the tumour extend beyond the bounds of the corpora quadrigemina and invade the fibres of the optic tract which pass through the external geniculate bodies, we may have either hemianopsia or blindness.

The central paths of the pupillary reflex are not fully known, though without doubt they are made up of several neurones of which the anterior corpora quadrigemina are a relay station. Thus, any destruction or indirect pressure in this neighbourhood would be sufficient to cause changes in the pupillary reflexes. Both of these cases had dilated pupils which could not be accounted for by diminished vision.

A question which even to the present day remains unsolved is the function of the posterior corpora quadrigemina. Have these structures any relation to hearing? Clinical and experimental evidence presents conflicting data. Kalischer and Rothmann working on trained dogs definitely proved that the destruction of the posterior corpora quadrigemina did not in any way affect the hearing of these animals, either for normal sounds or for varying tones. Rothmann thought that the posterior corpora quadrigemina are definitely related to hearing, but that their importance is secondary to that of the internal geniculate bodies which compensate for the function of the former. Weinland, in a clinico-pathological study, came to the conclusion that deafness in lesions of the posterior corpora quadrigemina depends upon destruction of the lateral lemniscus which leads to deafness in the opposite ear. The acoustic tract extends from the nuclei of the cochlear nerve in the pons to the opposite side by way of the trapezoid body, thence ascending in the lateral fillet to the posterior corpora quadrigemina, to the internal geniculate body and finally to the cortex of the temporal lobe. Spiller, Ruel, Starr, Ferrier, Collins and Hoppe, believe that the loss of hearing occurs only when there is coincident destruction of the lateral lemniscus. There are many case reports to substantiate this conclusion that an intact lateral lemniscus is essential for hearing.

In Cases 2 and 3 of this series, in which there was marked destruction of the corpora quadrigemina from invasion by a glioma, there was no loss of hearing. Unfortunately the lateral lemniscus was not studied in these cases, but was probably intact. Suffice it to say, both corpora quadrigemina were destroyed and hearing was present in both ears. On the whole it seems there is sufficient evidence to place the sense of hearing outside the functions of the corpora quadrigemina. In primary tumours of the pineal, or those arising from nearby structures, the loss of hearing is due to involvement of the lateral lemniscus, and thereby we may account for the discrepancy in case reports wherein the corpora quadrigemina are destroyed and hearing is not diminished. Because of these facts a definite function cannot readily be assigned to the corpora quadrigemina.

Owing to involvement of adjacent structures there may be signs referable to the dorsal longitudinal bundle, the lateral lemniscus, the red nucleus, the superior cerebellar peduncle, the motor and the sensory tracts (Turner and Bruns).

A review of the findings in Cases 2 and 3 shows a striking similarity to Case 1—a tumour of the pineal body. There are no signs differentiating these three cases. The sexual precocity, the very rapid onset of increased intracanial pressure and the dissociation of upward ocular movements—so frequently attributed to tumours of pineal origin—did not exist. The diminution of hearing frequently attributed to tumours of the corpora quadrigemina was absent. Pathologically these three cases were similar in the regions involved.

Case 2.—E. B., female, aged 21, admitted to Neuro-Surgical Service, University of California Hospital, April 14, 1920. A-20-20-70.

Complaint.—Headaches, nausea and vomiting; failure of vision; staggering gait.

Family history.—Essentially negative.

Past history.—Appendectomy two months previous to entering hospital.

Present illness.—Two years ago the patient began to complain of severe attacks of headaches and of constipation. The attacks of headaches and vomiting gradually increased in severity and frequency one year ago. Nine months ago she noticed that her left eye was displaced, and six months ago she found that this eye was almost blind. About this time she began to develop a staggering gait, stumbling from side to side. During the past three months she had "spells" when she lost control of herself and dropped; she did not lose consciousness, but she felt as if she had no power to help herself.

Physical examination.—Head, neck, chest and abdomen were normal.

Neurological examination.—The right optic disc was atrophic with blurred margins; the veins were markedly dilated. She was able to see fingers at eight feet. Left eye showed secondary atrophy with blurred margins and visual acuity was reduced to seeing objects immediately before the eye. The pupils were irregular, dilated, the right larger than the left and both reacted very sluggishly to light and accommodation. There was a definite exophthalmos of the right eye. The corneal reflex was diminished in both eyes. There was definite nystagmus in both eyes in looking to the right or left. There was a left central facial palsy. The palatal reflex was diminished. In the finger to nose test, there was a slight hesitancy on the right. The patient exhibited Rombergism, and in walking staggered from side to side, not falling in any particular direction. The deep reflexes were all present and equal and no pathological reflexes were observed.

Laboratory examination.—Blood, urine and fæces were negative. Spinal puncture not done. X-ray showed a flattened and wide sella with irregular absorption of the posterior and anterior clinoid processes. There was marked convolutional atrophy of the inner table of the left frontal region with widening of the sutures. Vestibular tests indicated an intracranial lesion in the region of the pons. It was possible that these subtentorial symptoms were due to pressure from a lesion in the anterior part of the brain. Patient died while in hospital.

Necropsy.—The specimen consisted of a soft, distorted, partly fixed brain. The pia arachnoid was not thickened or opaque. The sulci were normally disposed, the convolutions were somewhat flattened, partly on account of poor fixation, as well as hydrocephalus. The medulla had been removed The vessels remaining at the base and those in the Sylvian fissure appeared normal. The few remaining cranial nerves appeared normal. The hypophysis was not present. The hemispheres were separated and the brain-stem removed. The corpus callosum was thinned out and the lateral ventricles were enlarged by a moderate grade of hydrocephalus. The pineal gland appeared normal.

Invading the mesencephalon, extending backwards from near the posterior commissure, was a pultaceous, friable, grey mass of neoplastic tissue. Sections through the mid-brain showed this mass infiltrating and replacing the corpora quadrigemina, extending completely around the aqueduct of Sylvius and infiltrating the tegmentum in this region, slightly more on the left. The growth extended along the under surface of the valve of Vieussens, filling and distending irregularly the fourth ventricle and slightly infiltrating the cerebellar substance in the region of the vermis and apparently through the dentate nucleus.

Microscopical description.—Sections of the growth in the mid-brain region, and also as it extended into the cerebellum, showed it to be composed of small cells, varying somewhat in size, clustering about the strands of the connective tissue stroma and giving a somewhat papillomatous appearance to the tissue. There was a certain amount of pigment in the growth and in the adjacent cerebellar tissues, apparently the result of hæmorrhage. There was also some pressure atrophy of the adjacent cerebellum. On staining with phosphotungstic acid hematoxylin there were areas with a rich network of glial fibres.

Diagnosis.—Glioma, involving the corpora quadrigemina and valve of

Vieussens, and filling the fourth ventricle with slight extension into the cerebellum; internal hydrocephalus.

Case 3.—R. S., male, aged 19, admitted to Neuro-Surgical Service, Univ. of Penn. Hosp., April 29, 1922. 184, N.S.

Complaint.—Headache and failing vision. Convulsions.

Present illness.—Until two years ago the patient was perfectly well. About that time he developed attacks of severe vomiting. At first these occurred very frequently, but gradually their frequency and severity decreased. Six months ago he developed left-sided frontal headache which radiated posteriorly. He had three generalized convulsions, each lasting approximately half an hour and followed by a period of unconsciousness. In addition to these convulsions he had attacks of muscular twitching and weakness without loss of consciousness. On each occasion, he fell to the left side. His vision began to fail gradually, though he was still able to read.

Neurological examination.—There was a definite internal strabismus. The pupils were dilated and equal and reacted promptly to light and accommodation. The discs showed a marked pallor, especially on the temporal side, with blurred margin. The fields were contracted with a tendency to a bitemporal hemianopsia. The corneal reflex on the right was diminished. Hearing was normal. The deep reflexes on the right side were more active than those of the left. There were no pathological reflexes.

Laboratory examination.—Blood and urine normal. Spinal pressure, 24 mm. Hg. X-ray: The pituitary fossa was greatly increased in size, measuring 29 × 17 mm.; it encroached upon the sphenoidal sinus. Vestibular tests: vertigo was greatly shortened and past pointing was exaggerated. Patient died while in hospital.

Necropsy.—The consistency of the brain was normal. There was no asymmetry. About the base of the right frontal lobe and over the surface of the pons there was a small film of hæmorrhage. The basal vessels were normal. In the interpeduncular space was a large, bulging, spongy and granular mass about the size of a walnut and of soft consistence. It appeared under the optic nerves and chiasma and upon section was seen to be fairly well circumscribed. The mass filled the posterior part of the third ventricle, invaded and destroyed the corpora quadrigemina and extended into the posterior part of the thalamus. It compressed the aqueduct of Sylvius, thus causing marked dilatation of both lateral ventricles.

Microscopical description.—The cells were atypical in character and when well preserved they were large, acidophilic, with one or two peripheral nuclei. Generally, however, the cell body was indistinct, the nuclei were small, round and stained deeply. They were imbedded in a very loose network of fibres.

Diagnosis.—Glioma, involving the corpora quadrigemina, posterior portion of the third ventricle and posterior part of the thalamus. Internal hydrocephalus.

THIRD VENTRICLE.

The early symptoms of tumour involving the third ventricle are usually those of increased intracranial pressure. This is caused by obstruction of the foramina of Monro or of the aqueduct of Sylvius. In Cases 4, 5, 6, 7, 8, and 9, generalized pressure symptoms, as headache, nausea and vomiting, preceded all others by varying lengths of time. As the tumours increased in size they exerted their pressure upon the optic thalamus and the internal capsule. Thalamic symptoms are rare and did not occur in any of the cases here reported. Involvement of the internal capsule was of frequent occurrence. There was spasticity, moderate or marked, unilateral or bilateral, with the presence of over-active and pathological reflexes, or occasionally absent reflexes with flaccidity (Cases 4, 5, 7, 8, 9). Central facial palsy occurred in two cases (4, 6). With still greater growth of the tumour and with distension of the third ventricle, the roof area is encroached upon, and again the signs common to tumours of the pineal or corpora quadrigemina are found. The dorsal longitudinal bundle was involved in all these cases and the cerebellar tracts in three (5, 6, 7,). Mental symptoms frequently occur in tumours of the third ventricle (Henneberg, Mott and Barrett), but in this series there are only two cases that showed any mental impairment and this was not marked (6, 8). Pathological narcolepsy, due to involvement of the tuber cinereum, has been reported by Fulton, Bailey, and others.

Without doubt mental changes when they occur are the result of internal hydrocephalus. In a patient seen in this early stage presenting a clinical picture of increased intracranial pressure without any other symptoms a tumour of the third ventricle should be suspected, and efforts should be made to verify or disprove this diagnosis. It is unnecessary to await the onset of the neighbourhood signs; these are found only when the adjacent structures become involved.

In Case 4, localizing signs did not develop during the entire course of the patient's illness, which was nine months. Case 5 only developed localizing signs during the last five weeks of an illness of three years. These localizing signs were not of any great value, for they only referred to the pyramidal tracts. In Case 6 there was an unusually lengthy history of about eight years without any localizing signs. It is interesting that this patient had mental symptoms. In Case 7 there were not only signs of increased intracranial pressure, but evidences of pituitary disturbance. One year after the onset of pressure symptoms the patient developed signs of cerebellar disturbance. Case 8, a baby aged 3½ years, in addition to generalized intracranial pressure, developed signs of involvement of the roof five months after the onset of symptoms. Case 9, a boy aged 15, presented the shortest history of this series; in addition to his signs of increased intracranial pressure, he developed convulsive seizures.

Case 4.—P. B., aged 14, admitted to Neuro-Surgical Service, M.H. of the M.C. of V., May 16, 1925. A—4825.

Complaint.—Headache, nausea and vomiting.

Past history.—Essentially negative Menses had not commenced.

Present illness.—The patient stated that she had been subject to headaches all her life. During the last nine months these had become more severe and constant. Localized at first in the occipital region, they were later referred to the temporal region.

Accompanying the headaches was vomiting, not projectile in character, which had also increased in frequency.

For six months she had complained of periodical double vision. For three months she had been subject to dizziness and transient blindness on sudden movement.

For three months, in association with intense headache, she had been subject to "fainting spells." These began with shaking of both hands, inability to speak, rigidity, rolling upwards of the eyes and then transient unconsciousness.

At times she had seen objects like worms in the right of her field of vision.

She had become irritable and drowsy.

Physical examination.—The patient was emaciated. The thoracic and abdominal viscera were normal.

Neurological examination.—Bilateral choked discs, with swelling of 4D and hæmorrhages. Visual fields normal. Visual acuity O.S. $\frac{20}{30}$ and O.D. $\frac{20}{20}$. The pupils were widely dilated, irregular and unequal, the left larger than the right. They reacted very sluggishly to light and very slowly to accommodation. There was a slight right facial weakness of the central type and very slight weakness of the left arm. The deep reflexes were normal; no pathological reflexes were observed.

Laboratory examination.—Complete examinations of the blood and urine were normal. X-ray of skull showed a partial absorption of the dorsum sellæ with a very slight enlargement of the pituitary fossa. There was slight haziness of the posterior portion of the sphenoid sinus. Spinal puncture was not done. Ventriculography revealed that both the ventricles were markedly dilated without displacement, and there was a failure of passage of air from the right ventricle to the left. The conclusions from this procedure were that a tumour of the third ventricle must be eliminated before one of the posterior fossa could be considered. Air was then injected into the opposite side and again it failed to pass through the foramen of Monro. The patient died while in hospital.

Necropsy.—The skull was thinned and showed areas of convolutional atrophy. The brain beneath was under marked tension. Upon removal of the dura, the cortex showed marked atrophy of the convolutions. The brain was then removed with the dura, which was nowhere abnormally adherent to the bone. On palpation of the cortex it was noted that the ventricles were enormously dilated. The optic chiasma was markedly flattened and just anterior to this there was a yellowish solid protrusion which, on palpation, was of elastic consistency. Section of the brain showed that the entire third ventricle was filled with a semi-solid tissue which extended from the optic chiasma upward to the roof of the third ventricle, where it pressed upon the corpora quadrigemina and the pineal gland and extended posteriorly to the aqueduct of Sylvius. It did not invade the corpora quadrigemina nor the pineal, nor did it extend into the aqueduct of Sylvius, nor into the superior cerebellar peduncle. The tumour was of a homogeneous consistency and gelatinous appearance.

Microscopical description.—The tumour tissue was relatively vascular with well developed vessel walls. There were areas of coagulation necrosis. The cells consisted of small, round chromatin-poor nuclei with indistinct cytoplasm. There was a definite tendency for a perivascular arrangement of these cells, but this was not uniform.

Diagnosis.—Glioma (type undetermined) of the third ventricle. Internal hydrocephalus

Case 5.—E. M., female, aged 20, admitted to Neuro-Surgical Service, Univ. of California Hospital, April 29, 1923.

Complaint.—Headache and weakness of left leg.

Past history.—Measles and pertussis in childhood, otitis media and mastoiditis at the age of 2½. Appendicitis with appendectomy at the age of 4. Glands of neck incised, aged 12.

Present illness.—From the age of 10, the patient had frequent frontal headaches and attacks of nervousness. She had always been of a nervous temperament and frail physique. Three years ago she became very near-sighted and six months later developed severe sub-occipital headaches with attacks of nausea, vomiting and diplopia. The vomiting was not projectile. Five weeks ago she developed left parietal headaches and one week ago weakness of her left leg, tingling about the lateral portion of her nose, with numbness and paræsthesia about the external choanæ, paræsthesia in both hands and double vision.

Physical examination.—The patient complained of severe headaches and stiff neck, and kept her right eye shut to avoid seeing double. Small shotty glands were palpable on the right side of the neck. There was no evidence of enlargement of any other lymph glands throughout the body. The chest was small and the mammary tissue poorly developed. The lungs were normal. The heart was slightly enlarged downward and there was a soft, blowing systolic murmur over the apex and localized to this area.

Neurological examination.—There were bilateral choked discs of two dioptres with old and recent exudate and hæmorrhages. The left pupil was larger than the right, both were dilated and regular. The reaction to light was diminished, and the right pupil reacted less than the left. Vision, slightly diminished, was still sufficiently acute to read a newspaper. There was absolute loss of accommodation. There was a weakness of the right lateral rectus and a suggestion of central left facial weakness. She had bilateral nystagmus upon looking to the right and left. The left ear was deaf due to the mastoidectomy at the age of 2½. Dysdiadochokinesis more marked in the left hand. The finger-to-finger test and the finger-to-nose test were performed inaccurately, particularly on the left. The deep reflexes on the left were brisker than those on the right. There was a bilateral ankle clonus, more marked on the left. The left leg was weaker than the right. The neck was somewhat stiff.

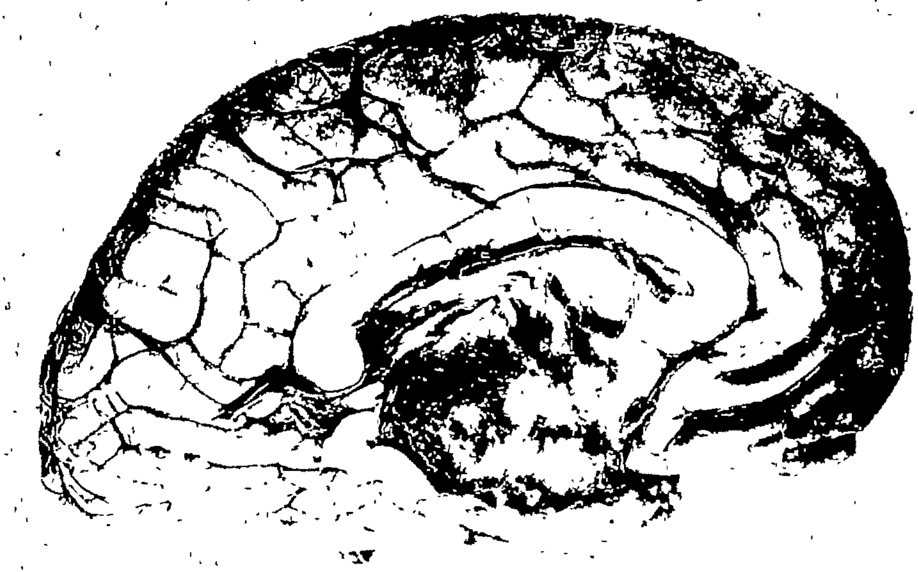


FIG. 2.—(Case 5.) Hemi-section of brain showing cystic mass filling the third ventricle.

Laboratory examination.—Blood, urine and X-ray normal.

The cerebrospinal fluid contained thirteen lymphocytes to the cubic millimetre; Pandy, Nonne, triple plus: sugar, one plus; colloidal gold and Wassermann negative. Patient died while in hospital.

Necropsy.—The skull over the vertex was slightly thinned, especially along the sutures. The dura was under marked tension and a small incision made accidentally resulted in rapid herniation of the cortex through it. Over the vertex of the hemispheres was a bluish-black discoloration, suggesting subdural hæmorrhage. The brain was removed together with the dura, the dura being nowhere abnormally adherent to the bone. There was marked flattening of the optic chiasma and just anterior to this was a mass of œdematous, slightly yellowish tissue, bulging through the incised dura. The cerebral convolutions were greatly flattened. A median longitudinal incision separating the hemispheres bisected a tumour mass measuring 4·5 by 5 cm. in its largest diameter, situated at the base of the brain in the region of the third ventricle and extending from the lamina terminalis anteriorly and to the level of the aqueduct of Sylvius posteriorly (fig. 2). It was situated immediately beneath the meninges at the base of the brain and extended upwards to the roof of the third ventricle, where there was a large cyst, measuring 1·5 cm. in diameter, with thin walls and filled with a gelatinous coagulated material. Just posterior to this large cyst were two smaller cysts of similar nature. The more dependent portion of the tumour was greyish, opaque and finely granular in appearance. Cross-section of the cerebellum at the level of the junction of the pons and medulla showed flattening of its right lobe and a deviation of the left lobe towards the right. There was a hæmorrhage into the substance of the left lobe, especially in the anterior portion. Cross section through the middle of the third ventricle showed symmetrically dilated lateral ventricles and the third ventricle distended with gelatinous tumour substance (fig. 3).

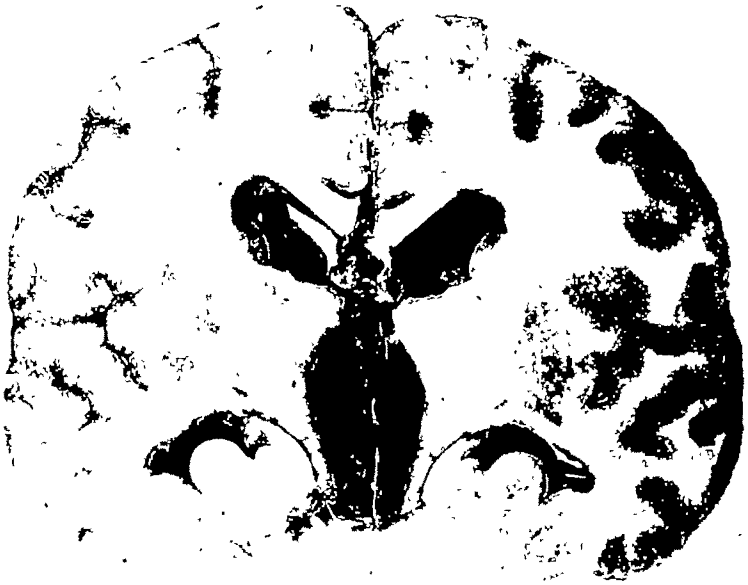


FIG. 3.—(Case 5.) Cross-section of brain showing symmetrically dilated lateral ventricles and the third ventricle distended with gelatinous material

Diagnosis: Glioma filling and distending the third ventricle. Internal hydrocephalus.

Case 6.—W. S., male, aged 26, admitted to Neuro-Surgical Service, Univ. of Penn. Hospital, May 11, 1924. 4516-1/2.

Complaint.—Headache, failing vision.

Past history.—Varicella and pertussis in childhood. Influenza in 1918.

Present illness.—For about seven or eight years the patient had suffered from sick headaches about once or twice a month. Six months ago these headaches became especially severe and were associated with nausea and vomiting. For the past four months he had been weak and unable to do his work on the farm For the past three months his vision had failed gradually, until at present he was unable to read. Occasionally he had been dizzy and felt as if he were being whirled about.

Physical examination.—The patient was a well-developed male ; in an area, 8 by 6 cm., over the rib margins to the right of the midline was a raised, soft, reddish area, covered by many minute blood-vessels.

Neurological examination.—Sense of smell was diminished on both sides. There were bilateral choked discs, of three dioptres in the right and four dioptres in the left eye. Visual acuity of the left eye was for large objects only, and in the right eye $\frac{5}{30}$. The pupils were dilated, sluggish to accommodation and fixed to light. Convergence was poorly carried out. Both visual fields were concentrically contracted. Mentality was slightly below average, memory decreased and the patient was of an apathetic, placid type. In walking, he deviated slightly to the right and in past-pointing deviated 4 in. beyond the object with his right hand.

Laboratory examination.—Spinal puncture not done. The X-ray showed atrophy of the dorsum sellæ and disappearance of the posterior clinoid process. There was slight convolutional atrophy and some rarefaction in the right occipital pole. Vestibular tests showed increased past pointing, slightly increased nystagmus, with nausea and vomiting. Vertigo was normal. Patient died while in the hospital.

Necropsy.—The convolutions of the brain were flattened. There were no abnormalities of the dura, pia or arachnoid. The posterior surface of the brain was normal in appearance. On palpation the cortex was rather soft, suggesting dilated ventricles. A hemisection of the brain revealed a large mass, reddish in colour and vascular, completely filling the third ventricle and pushing upward against the roof, obstructing the aqueduct and bulging into the foramen of Monro.

Microscopical description.—The tissue of the tumour was composed of numerous blood-vessels with areas of hæmorrhage and necrosis. These vascular tufts were covered with epithelial cells.

Diagnosis.—Papilloma of the choroid plexus of third ventricle, completely filling it. Internal hydrocephalus

Case 7.—S. G., boy aged 11, admitted to Neuro-Surgical Service, Univ. of Penn. Hospital, October 5, 1922. 216.

Complaint.—Failing vision. Ataxia.

Past history.—Measles, mumps, pertussis and varicella in childhood.

Present illness.—One year and a half ago, he began to have headaches associated with nausea and vomiting. His vision began to fail, but was relieved somewhat by the use of glasses. For the last year he has had polyuria and had gained about 15 lb. in weight. Six months ago he had an attack which he called "hysterics." In this attack, which only lasted a few minutes, he was unable to say what he wanted to, and could not express himself clearly. Later he developed a limp on his left side and when walking frequently staggered, particularly to the left. In the past two months his visual acuity had decreased and he had had diplopia. Vomiting and headaches had become more frequent.

Physical examination.—His build was suggestive of the Fröhlich's syndrome; he was abnormally fat, with a large head, small genitalia and absence of pubic hair.

Neurological examination.—There were bilateral choked discs of three dioptres in the right and four dioptres in the left. The pupils were dilated and reacted slowly to light and convergence. The field showed a slight restriction of the temporal area. He was able to read print. Dysmetria and dysdiadochokinesis were present on the left, with a tendency to stagger to the left in walking. The deep reflexes were hyper-active on the left side, with a Babinski plantar response and ankle clonus on that side.

Laboratory examination.—Spinal pressure 30 mm. Hg. X-ray: The pituitary fossa was enlarged, measuring 16 mm. by 14 mm., with depression of the floor. There was considerable widening of the sutures and convolutional atrophy. Vestibular tests: Vertigo and past pointing were almost normal. There was evidence of pressure on the brain, but no evidence of a local cerebral lesion. The responses for nystagmus were increased. Patient died while in hospital.

Necropsy.—The brain was removed within the dural envelope; there were no adhesions between the dura and the bone. On palpation the brain felt soft owing to dilatation of the lateral ventricles. The arachnoid was slightly thickened. Posteriorly, the base of the brain appeared normal except that in the interpeduncular space there projected a large irregular mass from the region of the third ventricle. On hemisection of the brain, there was seen a tumour, pale in colour, projecting into the third ventricle and distending it. This tumour was of about the size of a walnut and extended from the posterior knee of the corpus callosum a little to the right of the midline, invaded the thalamus and part of the right cerebral peduncle and then extended into the third ventricle. Both lateral ventricles were dilated.

Microscopical description.—There was marked overgrowth of glial cells which were well separated and small. There were no areas of necrosis and the capillaries were very numerous.

Diagnosis.—Glioma filling the third ventricle, invading the thalamus and part of the right cerebral peduncle. Internal hpdrocephalus.

Case 8.—T. S., child, aged 3½, admitted to Neuro-Surgical Service, Univ. of Penn. Hospital, January 4, 1922. P—40—22.

Complaint.—Headache and vomiting.

Past history.—Negative.

Present illness.—Nine months ago the child began to tire very readily on walking and had attacks of nausea and vomiting. In walking she frequently fell, though not to any particular side. Four months ago it was noticed that her head was increasing in size, and that while looking at objects both eyes turned inwards. Three months ago she became so weak she was unable to walk and since then has been confined to bed. Her eyes have converged inwards more frequently and her attacks of nausea and vomiting had increased.

Physical examination.—An ill-nourished child with a very large head.

Neurological examination.—There were bilaterally choked discs of six dioptres. Visual acuity was diminished, though she was able to see objects. Her pupils were dilated and reacted poorly to light. Both eyes were turned inwards. She was very drowsy, rather dull mentally and unable to move her legs. Her hands and arms could be moved voluntarily. All the deep reflexes were absent and there was a bilateral Babinski response. There was generalized hypotonia.

Laboratory examination.—Spinal pressure high. X-ray showed an enlarged head with separation of the sutures and convolutional atrophy. Patient died while in hospital.

Necropsy.—The dura and pia were normal. The convolutions were flattened and the brain was rather soft. In the region of the floor of the third ventricle was a protruding mass. Horizontal section of the brain showed a friable, well-defined mass filling the third ventricle, pressing upward on the roof and blocking the aqueduct of Sylvius. It compressed both cerebral peduncles. It measured 4 by 3 cm.

Microscopical description.—Tissue was composed of a homogeneous proliferation of glial cells.

Diagnosis.—Glioma distending the third ventricle. Internal hydrocephalus.

Case 9.—N. C., boy, aged 15, admitted to Neuro-Surgical Service, Univ. of Penn. Hospital, March 10, 1921. 6532.

Complaint—Headaches, vomiting, convulsions.

Past history.—Negative.

Present illness.—Three months ago, he began to have attacks of severe headaches, associated with nausea and vomiting. Shortly after this attack, he had a very severe convulsion, non-localizing in character and followed by a period of stupor.

Physical examination.—Negative.

Neurological examination.—He had bilaterally choked discs of six dioptres in the right and three dioptres in the left eye. The pupils were dilated and unequal, the left larger than the right. They reacted sluggishly to light. The left eye had a tendency to diverge. He was comatose. The biceps and triceps reflexes were absent in both arms, the patellar and Achilles reflexes were diminished and there was a left-sided Babinski response.

Spinal pressure 40 mm Hg. Patient died while in hospital.

Necropsy.—The cerebral convolutions were atrophied and the cortex felt cystic to palpation owing to dilatation of the ventricles. The dura was normal, but the pia was in numerous areas adherent to the cerebral cortex. Posteriorly, above the optic chiasma was a fluctuating mass which projected through the floor of the third ventricle and pressed upon the optic chiasma. A needle introduced into this mass revealed the presence of a turbid fluid which was sterile on culture. A median section through the brain revealed the extension of this mass upward to the roof of the third ventricle, which bulged into the superior aspect of the floor of the lateral ventricles, completely occluding the foramina of Monro. Both lateral ventricles were symmetrically dilated. (Fig. 4.)

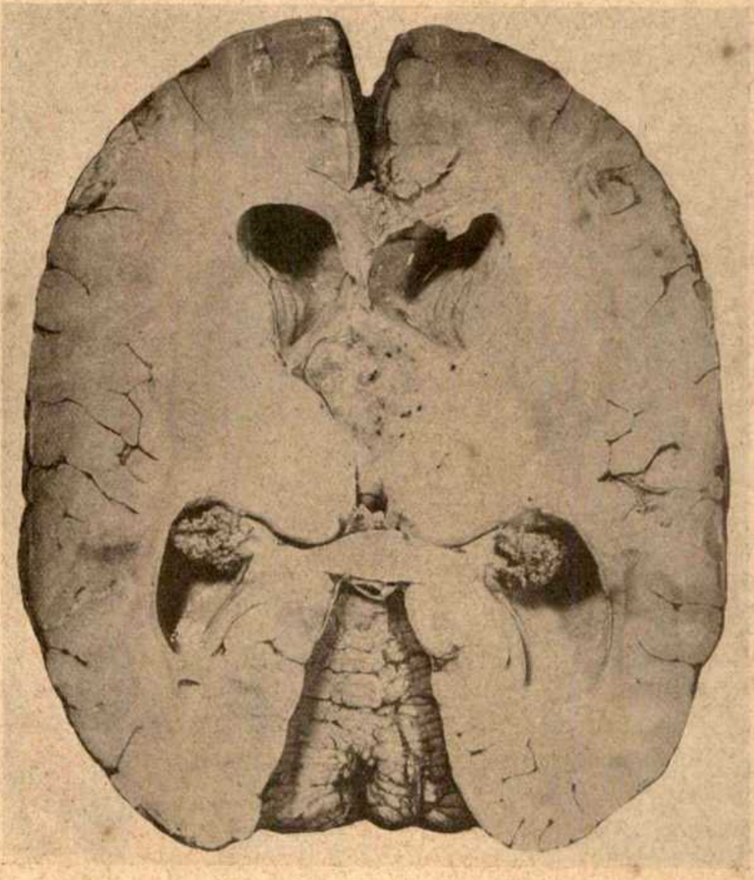


FIG. 4.—(Case 9.) Horizontal section of the brain showing the tumour filling the third ventricle and projecting into the dilated lateral ventricles.

Microscopical description.—Glioma with areas of cystic degeneration.

Diagnosis.—Glioma completely filling the third ventricle. Internal hydrocephalus.

SECONDARY INVOLVEMENT.

The cases hitherto considered are those in which the tumour took origin from the pineal body, the corpora quadrigemina and the structures adjacent to the third ventricle, with the major portion of the growth extending into this ventricle. Frequently tumours arising in other parts of the brain may produce similar symptoms from encroachment upon the same anatomical areas.

Large endotheliomata, arising from the falx in the frontal region, may extend backwards and completely occlude the third ventricle. Occasionally they give symptoms suggesting involvement of the posterior longitudinal bundle. An endothelioma arising in the frontal region frequently produces primary optic atrophy on the side of the tumour and a choked disc on the opposite side. Occasionally, however, these tumours may reach an enormous size, and displacement and obstruction to the circulation of the cerebrospinal fluid in the region of the third ventricle produces generalized increased intracranial pressure.

Rathke's pouch, hypophyseal duct tumours, and suprasellar endotheliomata, may reach such size as completely to occlude the third ventricle and invade the adjacent structures in the roof. Generally, tumours in this region grow downwards and involve the optic nerve by direct pressure (Case 12). In some of these patients a suprasellar shadow is evident in the X-ray plate. This will aid in differentiating such cases from those of primary pituitary neoplasm. When suprasellar calcification is present, it is pathognomonic of tumours in this area. There are certain types of suprasellar tumour which, instead of progressing downward and compressing the optic tract, grow upward, completely fill the third ventricle and occlude the foramen of Monro. Signs of involvement of the roof area may or may not be present, and, instead of the usual primary optic atrophy, choked discs occur from the concurrent generalized increase of intracranial pressure. This type of suprasellar tumour (Cases 10 and 11) is of importance from an operative point of view, for very frequently in exploring for tumours of Rathke's pouch by the usual transfrontal approach the growth is not visible in the operative field. Sudden death may occur in tumours of this type without any known cause.

In Case 10 there was no evidence of direct pressure on the optic tract. The child had choked discs early in the course of the disease, and later a secondary optic atrophy. Whether primary optic atrophy preceded the choked disc, or whether earlier in the course of the illness the patient had defects in the visual fields, was impossible to ascertain. From the history one is inclined to believe this was a tumour which grew upward rather than downward. On the other hand, the radiogram demonstrated a calcified shadow within the pituitary fossa, while the clinical signs were referable to involvement of the dorsal longitudinal bundle. It may be concluded that the tumour obstructed primarily the foramina of Monro, then growing upward encroached upon the roof of the third ventricle, and having its upward growth blocked became displaced downwards into the sella turcica. Fig. 5 shows that the entire third ventricle was filled. Another patient (Case 11), with a supraseller growth whereby the foramen of Monro was obstructed, is without doubt an example of an upward growing supraseller tumour. The optic nerves were not compressed, and evidence of cerebellar involvement with pressure in the region of the dorsal longitudinal bundle was present.

Idiopathic hydrocephalus and obstructive hydrocephalus, with a dilated third ventricle, may closely simulate a tumour of this region.

Subtentorial tumours in the region of the fourth ventricle or in the posterior portion of the cerebellum, may grow through the tentorium and involve the roof area. As a rule, these patients present manifestations of cerebellar involvement first, and later the signs indicative of roof involvement. The chronology of symptoms is very important, and care should be exercised in eliciting a history. The vestibular tests are of value in this differentiation.

Case 10.—E. S., girl, aged 9, admitted to Neuro-Surgical Service of Univ. of Penn. Hospital, February 18, 1927. 10217.

Complaint.—Inability to walk, loss of sight, headaches and vomiting.

Past history.—Child had chronic bilateral otitis media for two years between the ages of 2 and 4. She had the usual childhood diseases, as pertussis, measles, mumps and chicken-pox, and influenza in 1926.

Present illness.—Two and a half years ago, while going to school, the child struck the back of her head, but did not lose consciousness. About three weeks later the child began to complain of severe frontal headaches, most marked over the left eye and associated with vomiting. One and a half years ago she developed weakness in the left lower extremity, associated with "dizzy spells." One year later she developed convulsions, which were followed by severe attacks of headaches and vomiting. About this time her vision failed and she described visual hallucinations in the form of a sleigh drawn by reindeers crossing a snow-banked hillside. During the last six months her condition became worse. She was unable to get out of bed and had complete loss of vision. It was thought that her head had grown larger.

Physical examination.—There was marked hydrocephalus; her voice was coarse and she was extremely small of stature for her age.

Neurological examination.—There was bilateral post-papillitic atrophy with the disc margins still blurred and swelling of less than one dioptre. The arteries were small and tortuous. Her vision was limited to light perception in each eye. Her pupils were widely dilated and did not react to light. There was limited upward movement of both eyes beyond the horizontal plane, and slight limitation of movement to the left and downwards. There was a slight weakness of the right lower face and her hearing was better in the left ear than the right. The child was unable to hold her head up and the musculature was very poorly developed. There was slight spasticity of both legs and she was able to move the toes only of her left foot. Painful, thermal and tactile stimuli were recognized throughout the body. The reflexes were equal and active. There was no clonus but an occasional bilateral Babinski response. Mentality had deteriorated. She was unable to read or write.

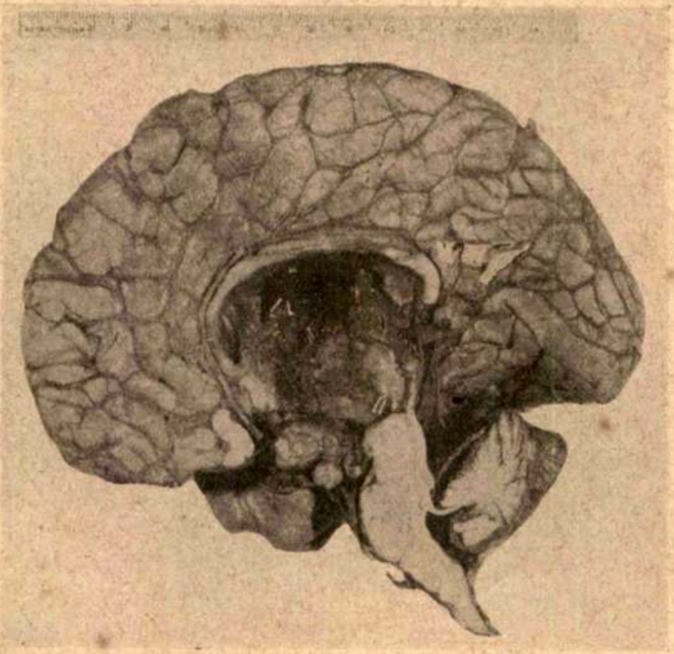


FIG. 5.—(Case 10.) Hemi-section of the brain showing the tumour distending the third ventricle and encroaching into the lateral ventricle. Note the presence of silver clips in the tumour.

Laboratory examination.—Blood and urine were normal. Spinal puncture not done. X-ray showed a marked degree of internal hydrocephalus with widening of the sutures; there was a calcification within an enlarged pituitary fossa, which measured 15 × 10 mm. Ventriculograms demonstrated an absence of a shadow in the region of the third ventricle. Vestibular tests gave no definite abnormality.

Operation by Dr. Grant. A trans-cortical incision was made into the ventricle. On opening the ventricle there was seen a yellow tumour, apparently cystic, bulging through the foramen of Monro. The tumour only loosely occluded the foramen and it appeared as though it may have acted as a ball valve. There was the usual perforation through the septum pellucidum, which occurs so frequently in hydrocephalus and accounted for the free communication between the ventricles, even though the tumour occluded the foramen of Monro. The cyst was ruptured and cholesterin crystals escaped. A large fragment of the tumour was then removed. A severe hæmorrhage occurred and was stopped with difficulty. Transfusion was performed and the child left the operating table in good condition. However, six hours later she collapsed and died, with a high pulse and respiratory rate and a temperature of 108° F.

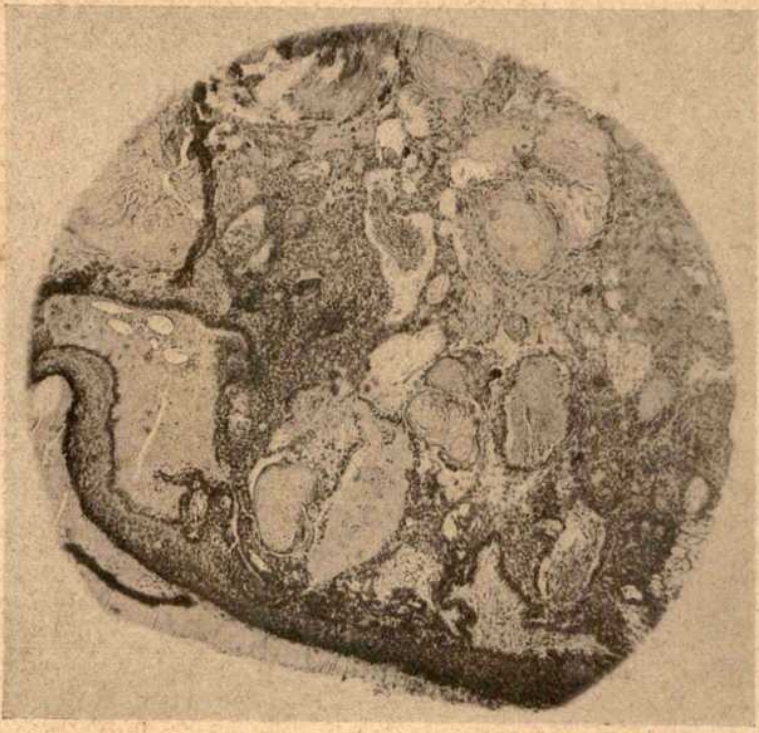


Fig. 6.—(Case 10.) Mixed tumour with the presence of embryonic tissue. Mag. 69.

Necropsy.—The dura and pia were normal. Over the cortex of the brain, on the left side, extending anteriorly from the Rolandic fissure, was a small incision. Posteriorly could be seen a tumour mass situated in the interpeduncular space. On longitudinal section (fig. 5), a mass of tumour tissue was revealed, extending from the floor of the third ventricle, completely filling the latter and entering the upper part of the lateral ventricle through the enlarged foramen of Monro. Although this tumour was originally confined to the third ventricle, the operative procedure allowed a great deal of it to bulge into the lateral ventricles.

Microscopical description.—The microscopic picture is one of great variability (fig. 6). There were embryonic tissue of cartilage, muscle and poorly formed epithelium.

Diagnosis.—Mixed tumour arising from the hypophyseal duct. Internal hydrocephalus.

Case 11.—J. C., male, aged 25, admitted to Neuro-Surgical Service, Univ. of Penn. Hospital, December 20, 1926; 9797.

Complaint.—Headache, blurring vision.

Past history.—Frequent attacks of epistaxis.

Present illness.—Following an attack of "intestinal influenza" six months previously, he began to complain of blurring of vision and headache. This headache was of a dull, aching character, situated on the left side of the head and occasionally radiating to the frontal and supra-orbital regions. Epistaxis recurred about every two weeks, lasting about half an hour. Associated with the headache were ringing in the ears, nausea and vomiting, the vomiting being of a projectile character. He had not worked since the onset of his symptoms and his headache was practically continuous. About one month ago his mother noticed that he "acted very queerly"; the right pupil became larger than the left and he moved his right arm up and down in purposeless movements. She also thought that his memory had depreciated and he had become very drowsy. Diplopia was present for the past two weeks.

Physical examination.—Essentially negative.

Neurological examination.—There were bilateral choked discs with four dioptres of swelling, hæmorrhage and exudate. The pupils were irregular and dilated, the right larger than the left. They reacted very sluggishly to light. He moved his hands almost continuously in a purposeless, athetoid fashion. He had bilaterally hyper-active reflexes, but no other reflex abnormalities. It was very difficult to hold his attention. He had great difficulty in standing, he leaned backward and was unable to stand on one foot alone; had dysmetria of his right hand and both feet and when he walked fell backwards. He had a moderate, generalized hypotonia and a positive Romberg.

Laboratory examination.—Blood and urine were normal, the blood and spinal fluid Wassermann negative. X-ray: atrophy of the anterior and posterior clinoid processes, with some depression of the floor of the pituitary fossa. Ventriculograms revealed symmetrical lateral ventricles with complete absence

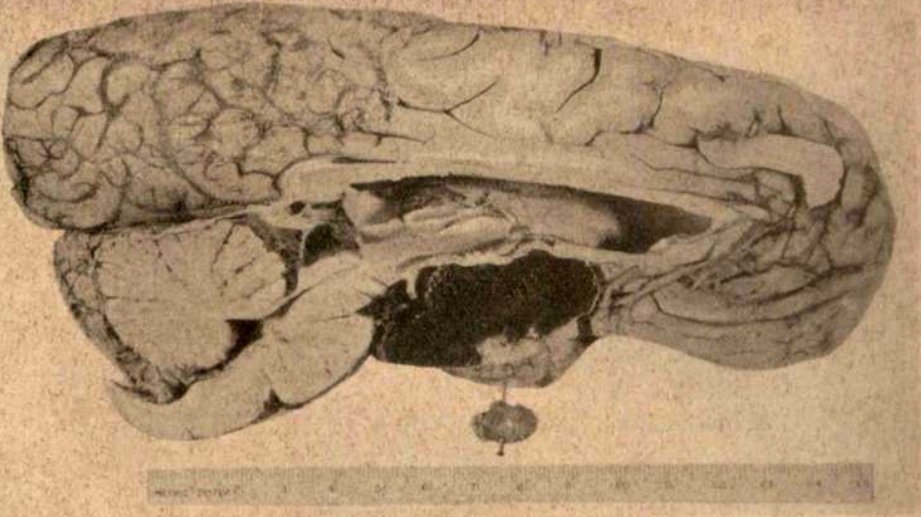


FIG. 7.—(Case 11.) Hemi-section of brain showing encapsulated tumour completely filling the third ventricle.

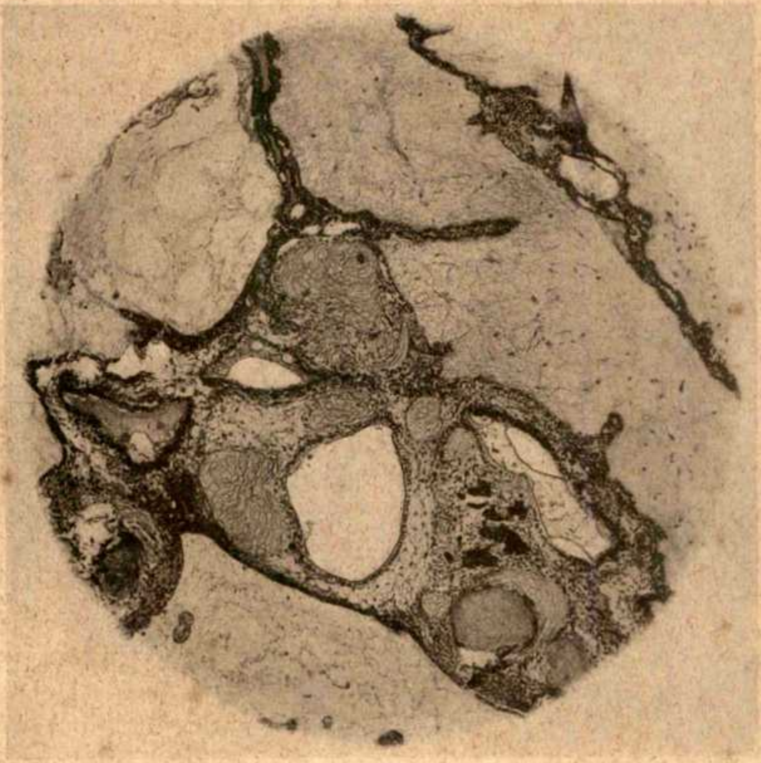


FIG. 8.—(Case 11.) Adamantinoma of the hypophyseal duct. Mag. 69.

of the third ventricle shadow in all plates. Vestibular tests incomplete, due to condition of patient. Patient died while in hospital.

Necropsy.—The dura was normal, the pia arachnoid was slightly thickened and milky over the entire cortex. There was moderate œdema of the brain. The vessels over the surface of the brain were normal. The interpeduncular space was distended by a large green tumour mass which filled the entire space. It lay against the anterior surface of the pons and extended forward to involve the optic chiasma; stretched over the posterior part could be seen the third nerve. On section this green mass was found to be encapsulated and of elastic consistency, measuring 5 × 2 cm. (fig. 7). Anteriorly, the capsule of the tumour invaded the sheath of the optic nerve. The basal portion was infiltrated by a small, cheese-like mass.

Microscopical examination.—There was a very small amount of tumour tissue surrounded by a homogeneous acid-staining material (fig. 8).

Diagnosis.—Adamantinoma of the hypophyseal duct, invading the third ventricle. Internal hydrocephalus.

Case 12.—M. K., female, aged 50, admitted to Neuro-Surgical Service, Univ. of Penn. Hospital. 7434.

Complaint.—Dimness of vision.

Past history.—She had measles, mumps, pertussis and malaria in childhood, typhoid fever in 1903, and influenza in 1918.

Present illness.—Nine months ago, the patient noticed a dimness of vision. Seven months ago she was able to read headlines only of newspapers. Six months ago she could not recognize a person across the street and there seemed always to be a haze before her eyes. At this time, while walking in the street, she suddenly thought she was surrounded by big black dogs, but recognized this as a visual hallucination. She had never noticed any decrease in her visual fields and she found that her visual acuity was better when she first began to read. She had had occasional bitemporal headaches, frequently radiating to the occipital region. She was fond of sweets, drank about two quarts of water each day and frequently had to void urine every half hour. Her appetite was ravenous, and in the past six months she had gained 50 lb., weighing 243 lb. at present. Her menopause had occurred a year ago.

Physical examination.—A very obese female.

Neurological examination.—Discs of yellowish colour; pupils irregular, right larger than the left, reacting poorly to light and not to convergence. Vision $\frac{6}{22}$ in the right eye and $\frac{6}{15}$ in the left eye. There was diplopia when the object was within convergence distance.

Laboratory examination.—Blood and urine were normal. Spinal fluid: the Wassermann test was negative and it contained 15 lymphocytes and 22 red blood-cells to the cubic millimetre. Pressure 20 mm. X-ray of head negative; pituitary fossa normal, 11 by 9 mm. Basal metabolism minus 21. Vestibular tests showed exaggerated past pointing and exaggerated nystagmus.

On the second entry, one month later, vision had decreased in the left eye to $\frac{6}{30}$ and in the right eye to $\frac{6}{22}$. Her fields showed a left homonymous hemianopsia. Basal metabolic rate minus 23. A transfrontal craniotomy was performed but nothing was found, and a sub-temporal decompression was later done. Six months later she again reported to the hospital and said that her vision had greatly improved; she still ate enormously, passed enormous quantities of urine and drank large quantities of water. The skull defect did not bulge.

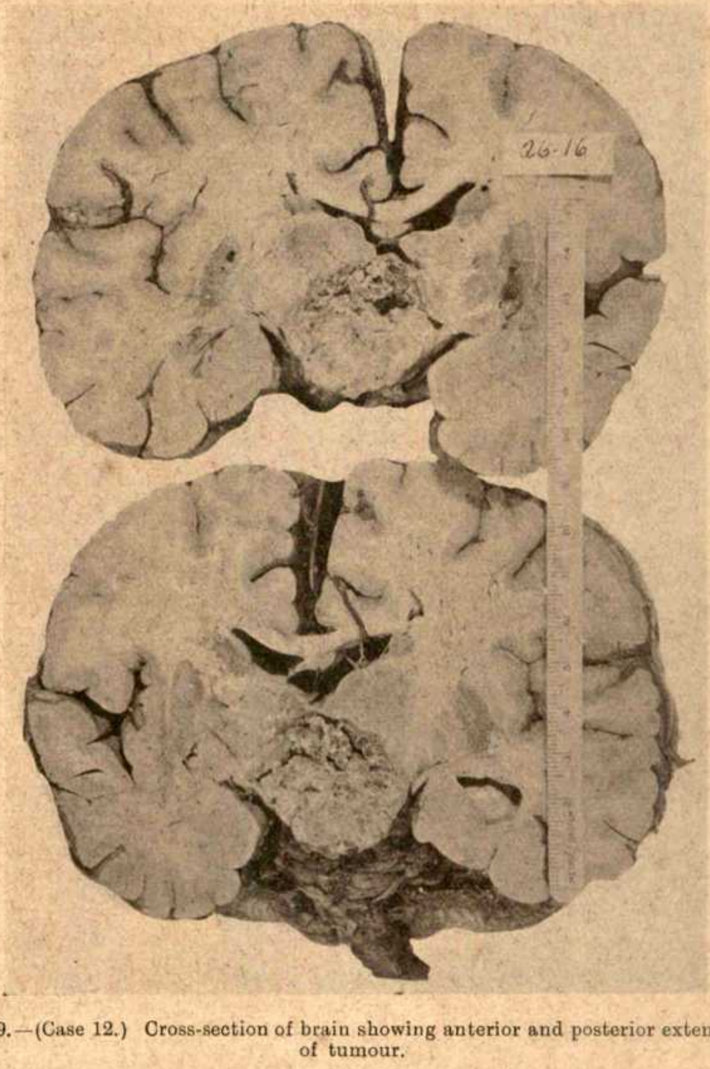


FIG. 9.—(Case 12.) Cross-section of brain showing anterior and posterior extensions of tumour.

On a third entry, one year after the first, the patient was semi-stuporous. Her physical signs were otherwise unchanged. Rather suddenly she became cyanosed, her blood-pressure could not be measured, her respiration became rapid and she died.

Necropsy.—In the interpeduncular space there was a hard mass. Over the left side was a hæmorrhagic area which extended into the occipital lobe. The convex cerebral surface presented a flattening and widening of the convolutions. The pia was of a slightly milky appearance. The surface was irregular and on it were cystic masses of irregular appearance. The mass pressed on the optic chiasma and optic tracts and occluded the infundibulum. It was larger in volume on the left side (fig. 9).

Microscopical examination.—The tumour consisted of narrow bridges of connective tissue and vessels covered by one or more even layers of cuboidal epithelium. In places there was a diffuse growth of cells without limit or arrangement. The bridges of epithelium were separated by a pinky staining homogeneous material. The structure was typical and could hardly be distinguished from that of an adamantinoma of the jaw. The anterior lobe of the pituitary was not enlarged and the cells took acid stain. The posterior lobe was slightly enlarged and contained some recent hæmorrhage (N. W. Winklemann).

Diagnosis.—Adamantinoma of the hypophyseal duct, involving the third ventricle. Hyper-activity of the anterior lobe of the pituitary; hæmorrhage into the posteriorlobe; hæmorrhage over the cortex of the brain. Internal hydrocephalus.

Clinical Findings.

Incidence according to sex.—In this series of cases, there were five males and seven females; thus no conclusion can be drawn with regard to sex predominance.

Age from onset of symptoms.—The majority of these patients developed their symptoms in the first, second and third decades, there being three in the first decade, four in the second decade, and four in the third decade. Only one case occurred in the sixth decade, this being an adamantinoma of the hypophyseal duct. Hence it may be concluded that tumours in the mid-central region occur predominantly in childhood and youth.

The initial symptoms in all these cases, except Case 12, were those of a generalized increase of intracranial pressure, such as headache, nausea and vomiting. Case 12 was an adamantinoma of the hypophyseal duct involving the third ventricle, growing downwards and compressing the optic nerves, thus causing blindness. Headache was a prominent symptom and was definitely localized in eight cases; of these eight cases five complained of frontal, two of bitemporal and one of occipital headache. In two of the cases with frontal headache the pain radiated into the parietal and sub-occipital regions.

The duration of the illness from the onset of the initial symptoms varied greatly. The shortest period was three months, in a case in which a glioma filled primarily the third ventricle; and longest period was eight years, also a similarly located glioma.

Subjective symptoms.—The subjective symptoms of these patients, in addition to those of generalized increase of intracranial pressure, were failing vision (seven cases), and diplopia (five cases). Cerebral cortical involvement demonstrated itself in a variety of symptoms. In two patients there was mental impairment; in one patient irritability; three patients had generalized convulsions; two patients had aphasia, and two patients visual hallucinations. Doubtless these cortical symptoms were the result of increased intracranial pressure (Hoppe, Weisenburg, Horsley). It will be observed that the mental symptoms frequently ascribed to tumours in the third ventricle occur on a parity with other cortical symptoms. Three patients complained of dizziness, and one patient of ringing in the ears.

OBJECTIVE NEUROLOGICAL FINDINGS.

Cranial nerves :—

(1) Olfactory.—In one case there was a diminished sense of smell in both nostrils.

(2) Optic.—Choked discs were present in all the cases except one. In this case a tumour arising from the hypophysial duct grew mainly downwards to compress the optic nerve.

(3, 4, 6) Oculo-motor, trochlear, abducens.—By far the most important diagnostic sign and one which occurred more frequently than any other was involvement of the pupillary reflex arc. Little attention has been, however, devoted to the size of the pupils and differences in pupillary reactions in the diagnosis of tumours in these regions. All the patients had one or more of these ocular signs. Dilated pupils were present in ten of the twelve cases. Irregular pupils occurred in five, and unequal pupils in three patients. Failure of reaction to light occurred in two patients. Sluggish reaction to light occurred in eight patients. Failure of reaction to accommodation occurred in eight patients, in three the reaction to accommodation was sluggish, and five had incomplete Argyll-Robertson pupils, and two had definite Argyll-Robertson pupils. Restriction of ocular movements occurred in ten patients, and consisted of the following defects: failure of outward movement of the eyes in three cases; failure of inward movement of the eyeballs in two cases; internal strabismus in two cases; limited upward movement in one case, and unilateral upward displacement of the eyeball in one case (Wilson, Horrax, Horsley, Bach, etc.).

(5) Trigeminal.—Corneal anæsthesia was present in two cases. This has been attributed to pressure on the ganglion by van Valkenburg and Monchy.

(7) Facial.—Only one patient had slight facial weakness.

(8) Acoustic division—showed no involvement. The *vestibular division* will be considered under the cerebellum.

(9, 10, 11, 12) There was no evidence of involvement of the glossopharyngeal, vagus, spinal accessory or hypoglossal nerves.

Motor system.—In nine of the twelve patients the motor system was affected, either in the form of a unilateral or bilateral weakness, paralysis and reflex changes.

Cerebellum.—Seven patients of this series presented the usual signs of cerebellar disease. Dysmetria occurred in six patients; ataxia in five and nystagmus in two. Two of these patients fell backward, which, according to von Sarbo and Williamson, indicates involvement of the red nucleus.

DIFFERENTIAL DIAGNOSIS.

It seems fairly conclusive that the symptoms and clinical signs of patients with tumours of the pineal body, corpora quadrigemina and third ventricle are very closely interrelated and may simulate each other. To attribute endocrine disturbance in the form of sexual precocity to the pineal is as yet unjustifiable. However, it may be allowed that while with the presence of sexual precocity a pineal tumour should be considered the more probable, without it a pineal tumour cannot be excluded. Failure of conjugate movement upward of the eyes above a horizontal plane cannot be considered pathognomonic of tumours of the pineal, though it is of frequent occurrence with tumours arising primarily from this structure. It should be looked upon rather as a sign of mid-brain involvement.

The functions of the corpora quadrigemina have not been yet fully elucidated; it is only on secondary involvement of the lateral lemniscus that disturbances of hearing occur. Tumours of Rathke's pouch may occasionally grow upward without compressing the optic tracts and produce signs very similar to those usually attributed to pineal tumours.

Signs of cerebellar involvement are present in this group of cases and very often lead us to suspect a tumour in the posterior fossa.

The chronology of the history is of extreme importance in the differentiation of these lesions from those of the posterior fossa. Tumours involving the mid-central region present cerebellar signs late in the course of the illness, whereas tumours which originate primarily in the cerebellum give their characteristic symptoms early in the course of the disease. This point is of extreme value in the differentiation of the tumours arising in the mid-central region and those arising sub-tentorially when an accurate history can be obtained.

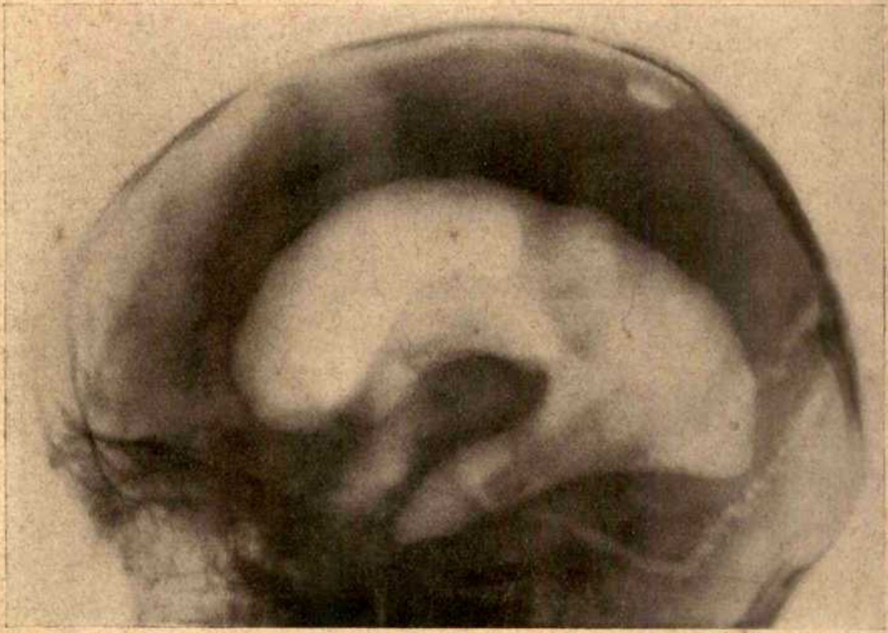


FIG. 10.—(Ventriculogram.) The lateral ventricles are symmetrically dilated and there is a definite shadow showing an air-filled third ventricle, Diagnosis: Tumour of the posterior fossa.

Ventriculograms and ventricular estimation.—For the differentiation of mid-central tumours from those of the posterior fossa, and for the differentiation of mid-central tumours from each other, a ventriculogram is of extreme value. Symmetrically dilated ventricles with signs of cerebellar disease are not sufficient evidence for a diagnosis of a tumour in the posterior fossa, nor is a cerebellar decompression indicated. In the cases herein reported, five presented such pictures (1, 2, 5, 6, 7) and four others (3, 4, 8, 9), though without signs of cerebellar lesions, suggested tumour in the posterior fossa. Cases 11 and 12 were of suprasellar origin, while Case 10 was definitely diagnosed as tumour of the third ventricle and operated upon as such.

When confronted with symmetrically dilated ventricles, with or without signs of a cerebellar lesion, it is important to eliminate a mid-central supratentorial tumour, and this should always be considered in the diagnosis. If in performing a ventricular estimation symmetrically dilated ventricles are found, the patency of the foramina of Monro should then be tested by the introduction of a dye in one ventricle and its appearance-time noted in the opposite ventricle. If one ventricle is injected with a small quantity of air the rotation of the head to the opposite side also may disclose a foraminal block. The ventriculogram will show a dilated lateral ventricle. Partial ventriculography wherein only small quantities of air are injected will not fill the third ventricle

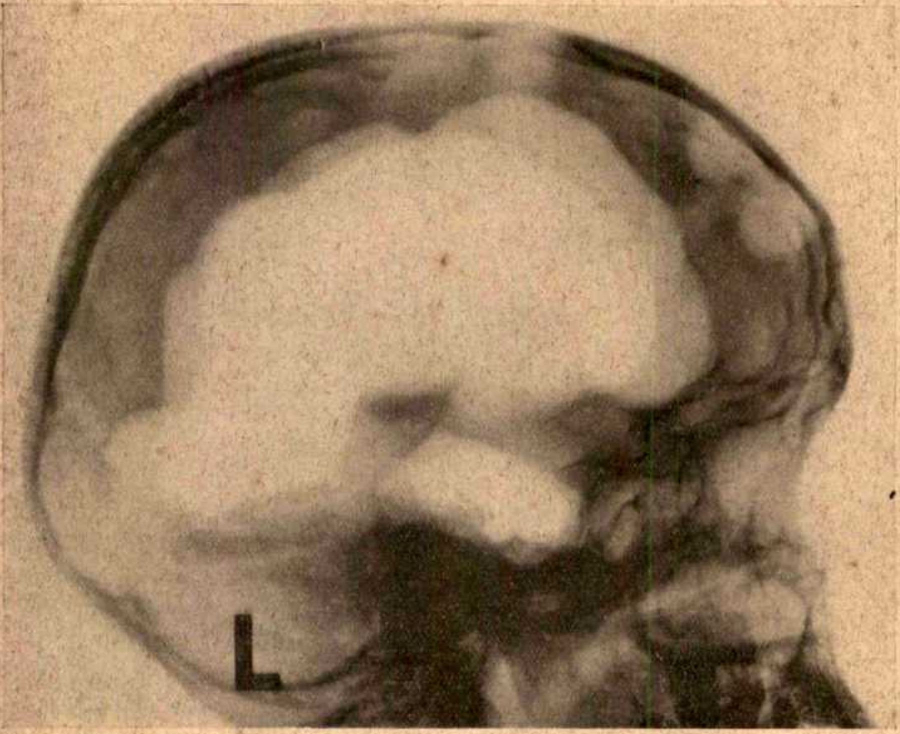


FIG. 11.—Ventriculogram. The lateral ventricles are symmetrically dilated but the third ventricle is not filled with air. Diagnosis: Third ventricle tumour.

sufficiently to make it visible on the plate. If both ventricles be filled with air, there will be sufficient air in the system to fill the third ventricle (fig. 10). If when both ventricles are dilated the third ventricle is not filled, and one is sure of proper technique in the performance of ventriculography, we must consider a block of the foramina of Monro, or the existence of a tumour filling the third ventricle (fig. 11). If the third ventricle is partially filled and there is evidence of distortion in the roof region, with bilateral dilated ventricles, we must suspect a tumour involving either the pineal body or the corpora quadrigemina.

VESTIBULAR TESTS.

In recent years the vestibular tests carried out by experienced observers and considered in conjunction with the neurological findings have proved of great aid, particularly in the classes of tumours under consideration. When the neurological signs are present, the commonest error of diagnosis has been to place these tumours subtentorially. A paper, as yet unpublished, by Fisher and Glaser, indicates that the findings of the vestibular tests can make this differentiation clearly. Not only can they place the lesion supratentorially, but they can also very often accurately localize its position.

SURGERY.

The surgery of this region has been long discussed; the earliest references are those of Krause in 1907. He states that the corpora quadrigemina had not been, as yet, the subject of surgical treatment. He believed it possible to interfere surgically by attacking that region through the posterior fossa of the skull by advancing between the cerebellum and the cerebrum. Not only tumours of the corpora quadrigemina, but pineal tumours and tumours of the posterior end of the corpus callosum, could be reached by a similar approach. In 1910 Gordon Holmes, discussing a paper by Hinds Howell, believed that pineal tumours might be susceptible of surgical approach. Sir Victor Horsley, at the same time, made the statement that a supratentorial access to the pineal region might be feasible. In 1913 Herman Rorschach, reporting a case, decided that there were two means of approaching this area, one by way of the cerebellum through the tentorium and between the hemispheres; the other by the supratentorial approach between the falx and the hemispheres. The posterior part of the corpus callosum should be separated, and then by transverse incision the corpora quadrigemina would be exposed. They operated upon one patient by this route, but did not discover a tumour. The patient recovered. Poussepp, in 1914, approached a tumour of the pineal by the tentorial route, but the patient survived only a few hours. In 1921, Dandy published an operative procedure similar in all details to that of Rorschach. By this means he removed two pineal tumours, one a tuberculoma, the patient surviving eight months, and the other a probable pinealoma, with death in forty-eight hours. In 1924, Howard Naffziger suggested an ingenious way of approaching tumours of this area. Utilizing the fact that all tumours of this area caused bilateral hydrocephalus with tremendously dilated ventricles and a thinned and avascular cortex, he suggested an osteoplastic flap uncovering the frontal lobe. By elevating the frontal lobe and incising the cortex beneath, he could enter the lateral ventricle, and, through the dilated foramen of Monro, the third ventricle. By this method he successfully removed a third ventricle tumour, the patient surviving the operation. In one of the cases herein reported Dr. Francis Grant partially removed a tumour in a practically moribund child. It appeared that this method of approach was feasible and worthy of consideration in all cases.

SUMMARY.

(1) Tumours of the pineal, corpora quadrigemina, and third ventricle present closely allied neurological signs due to the fact that the same anatomical structures may be involved in each case.

(2) No clinical evidence as to the function of the pineal or corpora quadrigemina is provided by these cases.

(3) Signs of involvement of the oculo-motor apparatus, the chronology of events, and ventriculographic and vestibular investigations are important aids to diagnosis.

(4) Surgery is indicated in all these tumours.

ACKNOWLEDGMENT.

I wish to thank Dr. Charles H. Frazier for his many valuable suggestions and his permission to utilize cases from his clinic; Drs. Ravdin, Spiller and Winkelman, for their helpful assistance; Dr. H. C. Naffziger, of San Francisco, and Dr. C. C. Coleman, of Richmond, Virginia, for permission to use cases from their services.

BIBLIOGRAPHY.

[1] Adler. "Extirpation der Epiphyse," *Arch. f. Entwicklungsmechan. d. Organ.*, 1914. **40**, 1.

[2] Bach, L. "Zusammenfassende Darstellung und kritische Betrachtung der Erkrankungen der Vierhügelgegend und der Zirbeldrüse mit specieller Berücksichtigung der ocularen Symptome," *Zeitschr. f. Augenheilk.*, 1899, **1**, 315.

[3] *Idem.* "Symmetrische Augenmuskellähmung.—Ein Beitrag zur Lokalisation im Oculomotoriuskern," *ibid.*, 1900, **3**, 307.

[4] *Idem.* "Die okularen Symptome bei Erkrankungen des Kleinhirns, der Vierhugel und der Zirbeldruse," *ibid.*, 1902, **8**, 213.

[5] Bailey, P. "Concerning Cerebellar Symptoms produced by Suprasellar Tumors," *Arch. Neurol. and Psych.*, 1924, **11**, 137.

[6] Bailey, P., and Bremer, F. "Experimental Diabetes Insipidus," *Arch. Int. Med.*, 1921, **28**, 773.

[7] *Idem.*, *idem.* "Experimental Diabetes Insipidus and Genital Atrophy," *Endocrinology.* 1921, **5**, 761.

[8] Bailey, P., and Jelliffe, S. E. "Tumours of the Pineal Body," *Arch. Int. Med.*, 1911, **8**, 851.

[9] Berkeley, W. N. "The Use of Pineal Gland in the Treatment of Certain Classes of Defective Children," *Med. Rec.*, 1914, **85**, 513.

[10] Bruns, L. "Zur differentiellen Diagnose zwischen den Tumoren der Vierhügel und des Kleinhirnes," *Arch. f. Psychiatr.*, 1894, **26**, 299.

[11] *Idem.* "Hirngeschwülste: Vierhügel und Zirbeldruse," *Neue Deutsche Chirurgie*, 1914, **12**, 78.

[12] Camus, J., Roussy, G., and LeGrand. "Un cas de diabète insipide par lésion de l'infundibulum," *Compt. rend. Soc. de Biol.*, 1922, **86**, 719.

[13] Camus, J., and Roussy, G. "Experimental Researches on the Pituitary Body," *Endocrinology*, 1920, **4**, 507.

[14] Dandy, W. E. "Extirpation of the Pineal Body," *Journ. Exper. Med.*, 1915, **22**, 237.

[15] *Idem.* "An Operation for the Removal of Pineal Tumors," *Surg., Gynec. et Obstet.*, 1921, **33**, 113.

[16] Evans, H. M. "Function of the Anterior Hypophysis," The Harvey Lecture, 1923, 1924, p. 212.

[17] Evans, H. M., and Long, J. A. "The Effect of Feeding Anterior Lobe of the Hypophysis on the Œstrous Cycle of the Rat," *Anat. Rec.*, 1921, **21**, 62.

[18] *Idem.*, *idem.* "Characteristic Effect upon Growth, Œstrus and Ovulation induced by the Intraperitoneal Administration of Fresh Anterior Hypophyseal Substance," *Proc. Nat. Acad. Sci.*, 1922, **8**, 38.

[19] Exner, A., and Boese, J. "Ueber experimentelle Exstirpation der Glandula Pinealis," *Deutsch. Zeitschr. f. Chir.*, 1910, **107**, 182.

[20] Foà, C. "Nouvelles recherches sur la fonction de la glande pinéale," *Arch. ital. de Biol.*, 1914, **61**, 79.

[21] *Idem.* "Hypertrophie des testicules et de la crête après l'extirpation de la glande pinéale chez le coq," *ibid.*, 1912-13, **57**, 233.

[22] Frankl-Hochwart, L. V. "Ueber Diagnose der Zirbeldrüsentumoren," *Deutsch. Zeitschr. f. Nervenheilk.*, 1909, **37**, 455.

[23] *Idem.* "Ueber Diagnose der Zirbeldrüsentumoren," *Wien. med. Wchnschr.*, 1910, **60**, 506.

[24] Fulton, J. F., and Bailey, P. "Tumours of the Third Ventricle; their Diagnosis and Relation to Pathological Sleep," *Journ. Nerv. and Ment. Dis.*, 1929, **69**, 1.

[25] Goetsch, E. "The Influence of Pituitary Feeding upon Growth and Sexual Development," *Bull. Johns Hopkins Hosp.*, 1916, **27**, 29.

[26] Haldeman, K. O. "Tumours of Pineal," *Arch. Neurol. and Psych.*, 1927, **18**, 724.

[27] Henneberg, R. "Ueber Ventrikel-und Ponstumoren," *Charité-Annalen*, 1903, **27**, 493.

[28] Hogner, P. "Die klinischen Erscheinungen bei Erkrankungen des 3 Gehirnventrikels," *Deutsch. Zeitschr. f. Nervenheilk.*, 1927, **97**, 238.

[29] Hoppe, H. "Tumor of the Corpora Quadrigemina," *Journ. Nerv. and Ment. Dis.*, 1912, **39**, 108.

[30] Horrax, G. "Differential Diagnosis of Pineal and Pontile Tumors," *Arch. Neurol and Psychiat.*, 1927, **17**, 179.

[31] Horrax, G., and Bailey, P "Tumors of the Pineal," *ibid.*, 1925, **13**, 423.

[32] Horrax, G. "Clinical Syndromes involving the Pineal Gland." In Barker's "Endocrinology and Metabolism," Appleton, 1922, **2**, 48.

[33] *Idem.* "Pineal Gland," *Arch. of Int. Med.*, 1916, **17**, 607.

[34] Howell, C. M. H. "Tumours of the Pineal Body," *Proc. Roy Soc Med.*, 1910, **3** (Neurol. Sect.), 65.

[35] Kallischer, Otto. "Experiments upon the Corpora-Quadrigemina of the Dog," *Sitzungsb. Koenig. Acad. Wissensch Berlin*, Phys math. Klasse, 1907, **21**, 8-10.

[36] Krabbe, K. "Pineal Gland; especially in Relation to the Problem of its Supposed Significance in Sexual Development," *Endocrinology*, 1923, **7**, 379.

[37] Marburg, O. "Die topische Diagnostik der Mittelhirnkrankheiten," *Wien. klin. Wochenschr.*, 1905, **18**, 532.

[38] McCord, C. P. "Pineal Gland in Relation to Somatic, Sexual and Mental Development," *Journ. Amer. Med. Assoc.*, 1914, **63**, 232.

[39] Monchy, S. J. R. de "Rhythmical Convergence Spasm of the Eyes in a Case of Tumour of the Pineal Gland," *Brain*, 1923, **46**, 179.

[40] Mott, F. W., and Barrett, J. O. W. "Three Cases of Tumours of the Third Ventricle," *Arch. of Neurol.*, 1900, **1**, 417.

[41] Nissen, W. "Zur Klinik der Tumoren der Vierhügelgegend," *Jahrb. f. Kinderh.*, 1901, **54**, 618.

[42] Orzechowski, C., and Mitkus, W. "Tumeurs du IIIe Ventricule," *Rev. Neurol.*, 1925, **2**, 1.

[43] Potts and Spiller. "Inability of Associated Movement to the Left," *Univ. of Pa. Med. Bull.*, 1903, p. 362.

[44] Pussep, L. "Die operative Entfernung einer Zyste der Glandula pinealis," *Neurol. Centralbl.*, 1914, **33**, 560.

[45] Roussy, G., Camus, J., and Le Grand, A. "Un cas de diabète insipide par lésion de l'infundibulum," *Compt. rend. Soc. de Biol.*, 1922, **86**, 719.

[46] Rothmann, M. "Zur Funktion der hinteren Vierhügel," *Neurol. Centralbl.*, 1907, **26**, 922.

[47] *Idem* "Ueber die Ergebnisse der Horprufung an dressierten Hunden," *Arch. f. Anat. u. Physiol.* (Physiol. Abt.), 1908, p. 103.

[48] Sarteschi, U. "Sindrome epifisaria 'macrogenitosomia precoce,'" *Pathologica*, 1912-13, **5**, 707.

[49] Smith, P. E. "Induction of Precocious Sexual Maturity," *Amer. Jrn. Physiol.*, 1927 **80**, 114.

[50] Smith, P. E., and Smith, I. P "The Effect of Intraperitoneal Injection of Fresh Anterior Lobe Substance in Hypophysectomized Tadpoles," *Anat. Rec.*, 1922, **23**, 38.

[51] Smith, P. E., Walker, A. T., and Graeser, J. B. "The Production of the Adiposogenital Syndrome in the Rat," *Proc. Soc. Exper. Biol and Med.*, 1923, **21**, 204.

[52] Souques, Baruk, and Bertrand. "Tumeur de l'infundibulum avec léthargie isolée," *Rev. Neurol.*, 1926, **1**, 532.

[53] Spiller, W. G. "Importance in Clinical Diagnosis of Paralysis of Associated Movements of the Eyeballs, especially in Upward and Downward Movement," *Journ. Nerv. and Ment. Dis.*, 1905, **32**, 417 and 497.

[54] Star, Allen. "Deafness due to Lesions in the Brain," *ibid.*, 1910, **37**, 401.

[55] Tilney, F., and Warren, L. F. "Contribution to the Study of the Epiphysis cerebri," *Amer. Anat. Mem.*, 1919, **9**, 7.

[56] Turner, W. A. "A Tumour of the Corpora-Quadrigemina with Impaired Eyeball Movements," *Brain*, 1892, **21**, 341.

[57] VON SARBÓ, ARTHUR. "Ein Fall von Stirnhirngeschwulst mit Beteiligung des Zwischen und Mittelhirngebietes," *Klin. Wochenschr.*, 1925, **4**, 168.

[58] VON VALKENBURG, C T. "Atrophia adiposo genitalis," *Ned. Tijd. v. Geneesk.*, 1920, **1**, 997

[59] WEINLAND, E. "Ueber einen Tumor del Vierhügelgegen und über die Beziehungen der hinteren Vierhügel zu Gehörsstorungen," *Arch. f. Psych.*, 1894, **26**, 363-380.

[60] WEISENBURG, T. H. "Third Ventricle Tumors," *Brain*, 1910, **33**, 236.

[61] WILLIAMSON, R. T. "Tumour of Corpora Quadrigemina," *Med. Chron.*, 1910, **52**, 328.

[62] *Idem.* "Tumour in the Region of the Corpora Quadrigemina," *Med. Press*, 1910, **90**, 561.

[63] WILSON, S. A. K., and RUDOLF, G. DE M. "Case of Mesencephalic Tumour with Double Argyll Robertson Pupil," *Journ. Neurol. and Psych*, 1922, **3**, 140.

[64] FISHER, L., and GLASER, M. A. "New Vestibular Complexes for Localisation of Lesions of the Brain." *Arch. Neurol. and Psych.*, 1929, **21**, 876.

NOTICES OF RECENT PUBLICATIONS.

Spezielle Histopathologie des Grosshirns. (Erster Teil.) By Prof. Dr. A. JAKOB. Pp. 412 with 266 illustrations. Leipzig u. Wien: Franz Deuticke. 1929. Price 40 M.

This is the first part of the second volume of Professor Jakob's book on "The Normal and Pathological Anatomy and Histology of the Cerebrum," which forms a part of the large "Handbuch der Psychiatrie," edited by Professor Aschaffenburg. The present volume has to do with the special pathology of the cerebral cortex in its relation to psychiatry. We are promised a second part which will include the extrapyramidal diseases and those lesions of the basal ganglia which are related to psychical disturbances and changes of behaviour. In the first chapter the author discusses the difficult problem of the extent to which mental disease is dependent on structural change in the brain. For him there is no sharp dividing line between the organic and the functional. Functional diseases are due to a reversible chemical or metabolic alteration in the neurons which cannot be demonstrated by the technique of histopathology, but which is yielding its secrets, one by one, to microchemical and biochemical investigations. Defective oxidation has been shown by Pighini and Marinesco to play a considerable part in these processes, and recent work on the blood-supply of the cortex and its relationship to the oxygen requirements of the cells of the various layers has cleared away some of the difficulties which have prevented a proper understanding of the problem. This introductory chapter does little, however, beyond stating the problem and indicating its complexity. What is already known of the pathology of mental diseases shows how varied may be the alterations in the brain. Not only the localization and distribution of the lesions, but their nature and the part of the neuron damaged vary from case to case and the possibilities of permutation and combination are legion. We must therefore be content to progress step by step, and not seek to solve the whole problem of mental disease by any single theory or conception, whether psychological or physiological.

The rest of the book is an example of this gradual progress. The individual diseases treated are tuberculosis of the cortex, syphilis in its various cerebral manifestations, African and American trypanosomiasis (these two very shortly), multiple sclerosis, and diffuse sclerosis (Schilder's disease). The important problem of cerebral syphilis has received such full treatment that there is little room for anything else in this volume, and many forms of cortical lesion which have a psychiatric interest remain to be treated, as well as those mental diseases in which the chief lesion falls on the basal ganglia.

Professor Jakob and his associates have paid particular attention to cerebral syphilis for many years, and the results of their work are summarized in this chapter of 260 pages, which is probably as full and comprehensive an account of the disease as can be found anywhere. There is a valuable section on the psychoses accompanying tabes which, under the name "tabo-paresis," are too often assumed to be of the same nature as general paralysis. Professor Jakob considers that this is usually but by no means always a true assumption, as the pathological basis of the cerebral symptoms varies widely. Another section deals fully with the difficult question of the pathogenesis of general paralysis. Here the author shows both a wide knowledge and a tolerant criticism of the work of others. He holds the modern view that both the infiltrative and the degenerative processes in the cortex are direct results of the presence of the spirochæte, but he is unable to give any very definite reason why the spirochæte should in one case cause a gummatous lesion and in another case an essentially degenerative process.

The book is well produced and beautifully illustrated. The use of type of varying size to indicate the relative importance of paragraphs might be more used in English textbooks. The illustrations are all excellent, and more care has been taken than in the first volume to arrange them so that comparable illustrations of the same area under different magnifications or with different staining methods are on the same page or face one another.

We look forward to the third volume of the book, which will, we hope, contain the index to the whole.

Lewandowsky's Handbuch der Neurologie. Ergänzüngsband ; 2te Teil, 2te Abschnitt. *Die Symptomatologie der Schussverletzungen der Peripheren Nerven.* von O. FOERSTER. 1929. S. 534. Price 86 M. 2te Teil, 3te Abschnitt. *Die Therapie der Schussverletzungen der Peripheren Nerven.* von O. FOERSTER. 1919. S. 212. Price 36 M. Berlin : J. Springer.

In a recent number of this Journal we reviewed the first of this series of volumes in which Professor Foerster dealt with the anatomy and physiology of the peripheral nerves. This was introductory to the two volumes under notice here, in which he discusses the symptoms and the treatment of gunshot wounds of the nerves, based on his investigation and treatment of nearly 4,000 war injuries. Though it is to be hoped that the author's experience will not be in the future required in this special field, the truly classical treatise which he has produced in these three volumes will undoubtedly influence teaching and practice for many years. There is no aspect of the subject, either clinical or surgical, that is not adequately dealt with, and the numerous problems of physiological or academic interest presented by injuries of the peripheral nerves are discussed equally fully. The chief value of the work lies in the presentation of his personal experience, but the widespread literature on the subject is fairly and critically reviewed too.

After short sections on the frequency and the nature of gunshot injuries of the nerves, he discusses the early and later structural changes produced by penetrating wounds and the regeneration of the fibres, and utilizes in his descriptions numerous striking illustrations, mainly from Spielmeyer. Even the degenerative and regenerative processes in the motor and sensory end organs are fully described. The next 150 pages are devoted to the motor disturbances produced by nerve injuries; in it every known symptom is fully discussed, most of the important features being illustrated by photographs or drawings. Disturbances of sensation are described in equal detail, including the phenomena present during recovery and the influence of concomitant vascular lesions upon them. One chapter that deserves special mention is that in which the variable distribution of the loss of different forms of sensation from lesions of the main nerve trunks and their branches is described and copiously illustrated. The last chapter of this volume deals with the various vasomotor, secretory and trophic changes associated with injuries of nerves.

Over 200 pages are allotted to the treatment of nerve injuries. Conservative methods directed to the prevention of overstretching of the paralysed muscles, and the formation of contractures and of changes in the joints are discussed, as well as the indications for operation and the most suitable operative procedures for individual cases. The results that may be expected from operation are set out from the author's own experience and the statistics of others.

This monumental work, for which the author deserves unstinted praise, will be indispensable to all engaged in the diagnosis and treatment of injuries of the peripheral nerves.

Comparative Neurology: A Manual and Textbook for the Study of the Nervous System of Vertebrates. By J. B. PAPEZ. Pp. 518, with 315 illustrations. New York: T. Y. Crowell Co. 1919. Price 6 dollars.

It is obvious that the structure of the brain can be best and most intelligently studied from the comparative point of view, for in many respects the nervous systems of the lower vertebrates is constructed on simpler lines, and this method of approach also gives instructive evidence of the relation between the mode of life of the animal and its nervous development. The author's aim has been to provide for the biologist and physiologist, as well as for the student of medicine, a textbook on the comparative anatomy of the nervous system, written mainly around the mammalian brain. It is not, as he suggests in his preface, merely a laboratory manual, though the student who studies it with specimens before him will undoubtedly learn more from it than he who reads it by his fireside.

The first two parts, which comprise the greater portion of the book, deal with the macroscopic and microscopic anatomy of the mammalian nervous system; in the third part the structure of the brains of the lower vertebrates is described more concisely. The text is clear and readable, and presents few divergences from the generally accepted views. It is copiously illustrated, chiefly by original drawings, though some are borrowed from well-known sources. A special feature of the illustrations is the use of the same legends for analogous structures in different species; this facilitates comparison, but he warns against an attempt at too rigid a homology. Several of the figures are drawings of dissections specially prepared to show anatomical relations as simply as possible, and there are many diagrams too. The book can be recommended as a simple and reliable textbook on the anatomy of the nervous system.

Die Neuropathologischen Syndrome. Von M. KROLL. S. 554, mit 216 Abbildungen. Berlin: J. S. Springer. 1929. Price 45 M.

The author describes the various symptom-complexes of nervous disease, firstly under the heading of motor, sensory and reflex disorders, and then upon a topographical basis. There are also chapters on vascular disease, neurosyphilis, meningitis, encephalo-myelitis, endocrine disorders, the angio-trophoneuroses and the neuroses.

The clinical descriptions are clearly written and comprehensive, and are well illustrated by original photographs. The author has embodied with remarkable completeness the great mass of recent observation on normal and abnormal reflexes and on the cerebral localization of symptoms.

In his effort to incorporate the modern applied physiology of the nervous system into the clinical framework of his subject the author has been less successful. This, perhaps, is inevitable, since the physiology of the nervous system is at present in a state of very active growth, and the majority of attempts to determine the functions of the different parts of the nervous system upon a clinico-pathological basis take too little account of modern advances in neuro-physiological doctrine, and even when they make contact with it they do not discard with sufficient thoroughness the vast amount of purely speculative opinion that has obtained currency in neurological clinical literature during the past twenty years. It is clear that any attempt to retain and to combine both, without a preliminary elimination of what is physiologically unsound, cannot be successful.

These difficulties are illustrated in the theoretical sections of the book dealing with motor symptom-complexes and with the sensory system.

Nevertheless, the author's failure to achieve a satisfactory synthesis of clinical, pathological and physiological observation does not lessen the value of his book as an up-to-date and concise account of the symptomatology of nervous disease.

Reflexmechanismus spastischer Lähmungen. Von O. LEIBOWITZ. S. 40. Heidelberg: Grosberger. 1928. Price 2 M.

The monograph is the first of a series to be published under the title of "Medizin in Einzeldarstellungen."

The author's theme is the physiology of the reflex phenomena of spastic paralysis, for which he attempts to formulate a generalization comparable with those of Wernicke and Mann in respect of paralysis and spasticity in hemiplegia.

His clinical material consists of forty-two cases of spastic paralysis of various clinical varieties, and the source to which he goes in the endeavour to find support for his theme is, almost wholly, German neurological literature. While much valuable work has been done on the physiology of the tendon-jerks, and upon the action currents in skeletal muscle, in the University of Heidelberg within the past few years, it is clear that an author who thus voluntarily restricts his sources of inspiration cannot present a balanced or modern account of his subject.

La Myasthenie. Maladie d'Erb-Goldflam. Par P. BOURGEOIS. Pp. 207. Paris: N. Maloine. 1929. Price 26 fr.

This monograph on myasthenia gravis fills a definite blank in neurological literature. It provides a complete history of the disease since it was first recognized, and gives a satisfactory review of its clinical features and of the pathological changes that have been described in association with it. The most interesting pages, however, are those on the electro-physiology of the myasthenic muscle, in which the nature of the so-called myasthenic reaction is analysed and numerous observations on the chronaxie and the action currents of the muscles are described. These observations prove that the myasthenic reaction is not specific for this disease, while other methods of electrical examination show that normal and myasthenic fatigue differ in degree only, not in nature. The author concludes that the myasthenic phenomena cannot be explained wholly by an affection of the muscles, and assumes a humoral disturbance in which one of the endocrine glands probably plays an important part.

This interesting monograph is unfortunately spoiled by many typographical errors and faulty pagination.

Epidemiology: Old and New. By Sir WILLIAM HAMER. Pp. 180. London: Kegan Paul and Co. 1928. Price 9s.

The author compares the behaviour of epidemics as seen in and from London during the past forty years with corresponding happenings in Sydenham's time.

The clinician who reads this book, as every clinician may do with profit, will early realize the great strides which the science of epidemiology has made within the past quarter of a century, and the revolutions which it is destined to work in our conceptions of the relationships existing between organisms and the diseases believed to be caused by them.

He will also find in its pages a philosophical outlook which is too rarely to be found in clinical writings.

To the neurologist in particular the consideration of the infective diseases attacking the nervous system in their possible relation to influenza, Sydenham's "standard fever of nature," must prove of great interest and importance. After a generation of clinical analysis and differentiation of the various symptom-complexes of infective nervous diseases the necessity for an attempt at synthesis will not be disputed.

The author's standpoint is expressed in the following statement: "From the epidemiological standpoint it is clear, then, that the epidemics affecting the central nervous system which have been under consideration all stand in close relationship to one another and to influenza. They are none of them "new diseases," though it must be agreed that in order to find parallel instances to the recently observed vagaries of encephalitis lethargica we have to hark away back for a number of years. . . . . The question has therefore to be considered whether epidemics, attacking different portions of the cerebrospinal nervous system, and therefore producing widely different symptom complexes, may be due to related viruses, or even to some one virus, producing effects of varying character, when operating upon communities exhibiting differing degrees of resistance to infection, or living under differing climatic or social conditions."

Little as a purely clinical training may dispose the reader to accept such a standpoint, the evidence upon which it is founded must be considered upon its merits, and these can have no more authoritative exponent than Sir William Hamer.

Clinique médicale des Enfants: Affections du Système nerveux. Par P. Nobécourt. Pp. 372. Paris: Masson et Cie. 1928. Price 45 fr.

The author records at length a series of clinical demonstrations of organic nervous affections of childhood. Case histories, signs and symptoms, treatment and prognosis are discussed at length and comprehensively. Clinical pathology and morbid anatomical findings are also considered in relation to clinically observed phenomena.

The demonstrations have already been published in various French medical periodicals, but their collection and publication in a single volume are amply justified and provide a volume of value and interest.

There is an extremely full index, but no table of contents.

Recent Advance in Neurology. By W. R. BRAIN and E. B. STRAUSS. Pp. 412. London: J. and A. Churchill. 1929. Price 12s. 6d.

Recent Advance in Psychiatry. By H. DEVINE. London: J. and A. Churchill. 1929. Price 12s. 6d.

These two volumes belong to a series, now in course of publication, the aim of which is to collect and put concisely the recent advances of our knowledge in various branches of medicine.

The first of them includes more than recent advances in neurology, in fact a large part of the material presented can be found in current textbooks of medicine and neurology. It is, however, a useful compilation for the student and for the practitioner to whom current literature is not available. Otherwise it deserves much praise, as the subjects chosen are dealt with clearly and concisely, and a considerable critical discrimination has been shown in their discussion. The greater part of the book is concerned with subjects of purely clinical interest, but certain chapters, as those on Posture and Tonus, Conditioned Reflexes and Sleep, are mainly physiological.

It was no easy task for the author of the second volume to correlate the recent work in a subject about the fundamental principles of which there is still much bitter dispute. Fully conscious of this, Dr. Devine has opened his survey with a discussion of the fundamental processes that underlie the related phenomena of behaviour. In so doing he attempts to find a place for all the physical incidents of an internal and external nature that play their part in the production of psychosis, and of those so-called psychological processes which are grouped together under the term states of consciousness. He makes the law of blastophoria a foundation stone of his thesis, and seems to place the centre of gravity of the psychosis in the realm of the somatic, but he does not neglect the more mental aspects of the study of psychiatry, in fact he refers fully to recent advances in the psychological and specifically psycho-analytical studies of the psychoses. But in his treatment of this branch of the subject he approaches the mind of the psychotic with the feeling that what light psychology may throw is likely to be dim.

For Dr. Devine's treatment of the physical problems of the psychoses nothing but praise can be given. He has marshalled the vast amount of facts on chronic infections, metabolic changes, and the treatment of G.P.I. by malaria in a masterly way. His chapter on the Biogenic Psychoses takes us beyond the rigid classification of Kraeplin to the more dynamic views of Bleuler, and the morphological correlations of Kretchmer.

Owing to the controversial nature of the basic principles of psychiatry this book is certainly not for the beginner. It will be, however, an excellent stimulus to the serious student and practitioner in psychiatry.

Medicine and the Man. By MILLAIS CULPIN. Pp. 67. Psyche Miniatures, Medical Series. London: Kegan Paul and Co. 1927. Price 2s. 6d.

Confronted by an imperfect world, Hamlet voiced his perplexities in the famous lines:—

> "The world is out of joint: O cursed spite,
> That ever I was born to set it right."

No such misgivings beset Dr. Culpin who, in face of the defects in medical thought and teaching deplored in his book, has sought, and apparently found, the facile consolations of wisdom after the event.

The burden of his theme is the "mental attitude which impels us to ascribe to physical causes morbid conditions in which no physical cause can be demonstrated, and in which the postulate of a physical cause leads only to a wrong handling of the situation." "Even when such error is avoided," he adds, "the diagnosis of a neurosis or a functional nervous disorder means the end of professional interest."

Dr. Culpin is singularly unhappy in the example he chooses to illustrate the first of these strictures, for it proves to be the case of a soldier who was thought to have structural heart disease and was dealt with accordingly, whereas the event proved that no such disease was present It was surely both irrelevant and unnecessary to write a book to tell us that such errors of diagnosis occur, or to deplore their unfortunate consequences, while his second stricture is little but the echo of a battle lost and won long since.

It is easy to make merry over the view, now universally discarded, that attributed "shell shock" to minute structural lesions in the brain, but when the condition first confronted the profession in the early days of the war it would have been a reckless assumption to label it a neurosis.

There is indeed some substance in the author's indictment of the treatment of the neuroses in textbooks of medicine, and of the tendency to diagnose physical disease in the absence of adequate evidence thereof, but no case is so good that it can dispense with balanced and dispassionate statement. With this Dr. Culpin fails to provide his readers.

Psychologie der Schizophrenie. Von Dr. JOSEF BERZE und Dr. HANS W. GRUHLE. Pp. 168. Berlin: Julius Springer. 1929. Price 16 R.M.

This monograph on schizophrenia is divided into a general and a special section. The first essay by Professor Berze discusses the basic cardinal symptom of the disorder as a distinguishing mark. This essay is, in other words, purely formal and should logically have followed Professor Gruhle's essay which deals with the characteristics of the schizophrenic reaction.

Both essays are deeply influenced by the psycho-analytic views on the psychoses, but full recognition is also afforded to Jung, Maeder, Bleuler, Minkowski and the French school.

Psychotherapie. Voraussetzungen, Wesen, Grenzen. Von HANS PRINZHORN. Leipzig: George Thieme. 1929.

Like all German writers on fundamentals, there is a tendency in this writer to overstate the philosophic gravity of the problems of psycho-pathology and of the therapeutic methods that spring therefrom. This, however, does not detract from the merits of this somewhat long book. The author in no wise spares the subject from the harshness of keen criticism, although his sympathies are almost entirely on the side of the freedom of psycho-pathology to develop along its own lines. Despite this standpoint, the author is in the main largely concerned with relating the views of the psycho-analytic school to general psychology and to theoretical biology.

On the whole a very thought-provoking book to be considered by all who are interested in foundations.

Ueber Umbau und Abbau der Sprache bei Geistesstörung. Von Dr. F. G. STOCKERT. Berlin: S. Klarger. 1929.

This monograph on the elaboration and disintegration of language in mental disorder covers the field in a very philosophical and systematic way. Chapter I deals with injuries to the function of expression and reviews adequately the researches on the affective element in language, starting with animal expression and thence to the language of children. This gives the right background to a consideration of fully-developed language and its disturbances. The next section concerns anomalies of the representative function. Thus, dealing first with the melodic and emotive elements, the author now considers the more formal or ideational content of speech. Finally, the function of interpretation and its disturbances is considered. The book is richly illustrated with references to the main reaction types of the insanities, organic and functional; and general literature from Goethe to Nietzsche is drawn upon for illustration and comment. Although the treatment has much in common with Head's psychological approach to aphasia, these investigations are not even mentioned. This omission is unforgivable in what is after all a serious study in the anomalies of speech.

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-91, Great Titchfield Street, London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I to XXIII inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.

SEPTEMBER, 1929.

CALCUTTA UNIVER
ec. No......
Book No.
LIBR

BRAIN.

PART 3, VOL. 52.

SUBACUTE COMBINED DEGENERATION OF THE CORD: SYMPTOMATOLOGY AND EFFECTS OF LIVER THERAPY.

BY C. C. UNGLEY, M.D., M.R.C.P.

AND

M. M. SUZMAN, M.D., M.R.C.P.

(*From the Royal Victoria Infirmary, Newcastle-upon-Tyne*)

THIS article recapitulates, with some modifications, the substance of our paper [24] in the *Newcastle Medical Journal*, of January, 1929.

The detailed tables have been omitted, and a comparative analysis of the cases before and after liver treatment takes their place. Most of the cases have been re-examined, and certain alterations have been necessary, due to changes which have occurred since the patients were last reported on four months ago. In addition, a detailed account of the symptomatology of the sixty-one cases has been included.

While the beneficial effects of liver diet in pernicious anæmia are well recognized, there seems to have been some doubt as to the value of this form of treatment in subacute combined degeneration of the cord. As far as can be gathered from the literature, which is reviewed elsewhere in this paper, no extensive series of cases has previously been reported on, and it would appear that there is considerable difference of opinion on the subject. Because of the doubts existing in this matter, investigations were carried out on all cases of subacute combined degeneration of the cord associated with this hospital since January, 1925; those admitted during the two years prior to the introduction of liver diet were included for purposes of comparison. The series comprises sixty-one cases, of which thirty have been treated by liver.

While our chief object was to determine the effects of liver treatment, an analysis of such a large series of cases of subacute combined degeneration of the cord has been found to contain many points of interest in the symptomatology of the disease. It is therefore proposed to divide the paper into two distinct parts, dealing firstly with symptomatology, and secondly, with the effects of liver therapy.

I.—SYMPTOMATOLOGY.

Before proceeding further, it is desirable to state what evidence has been considered necessary for a diagnosis of subacute combined degeneration.

No case has been included which has not shown definite signs of involvement of either the posterior or lateral columns of the cord, or of both sets of columns. Inco-ordination and ataxia from loss of muscle and joint sensibility, and in addition loss of vibration sensibility, are the signs which have been taken as evidence of posterior column involvement.

The "extensor" type of plantar reflex (Babinski's sign), with or without exaggeration of the deep reflexes and patellar or ankle clonus, have been accepted as evidence of degeneration of the pyramidal fibres of the lateral columns.

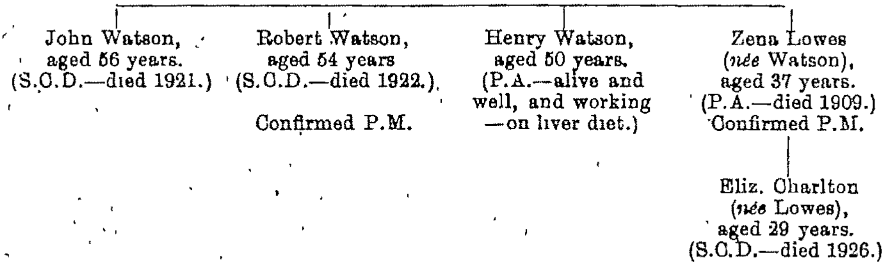
Numbness and tingling in the hands and feet, and slighter degrees of anæsthesia in the periphery, although important symptoms, as well as loss of knee and ankle jerks, have not in themselves been regarded as sufficient to warrant a diagnosis of subacute combined degeneration. A certain number of patients with pernicious anæmia exhibit these phenomena, and although we are aware that they probably indicate involvement of the peripheral nerves, or, as some believe, of the posterior columns, we have purposely excluded such cases from this series.

Incidence.—The total number of cases was 61. This shows that the disease is not as rare as some observers have been inclined to believe.

We cannot state definitely whether it is more common in this vicinity than elsewhere; however, a study of the geographical distribution might reveal some interesting facts.

The sexes were involved almost equally, 32 being males and 29 females. The ages varied from 29 to 65, the average age at onset being 45·3 years in males, and 44·3 years in females.

Heredity.—It is well known that cases of pernicious anæmia may occur in several members of a family, and similarly, it has been stated that subacute combined degeneration may have a familial incidence. Such cases have been reported by Hurst [8], Meulengracht [13], Dorst [4], Johannessohn [9], Liepelt [11], Tscherning [23]. In this connection, the record of the Watson family is interesting, as it shows multiple cases of both diseases co-existing in the one family. Two generations were involved, and in the second generation the disease occurred at an early age and was rapidly fatal.


John Watson, aged 56 years. (S.C.D.—died 1921.)
Robert Watson, aged 54 years (S.C.D.—died 1922.). Confirmed P.M.
Henry Watson, aged 50 years. (P.A.—alive and well, and working —on liver diet.)
Zena Lowes (née Watson), aged 37 years. (P.A.—died 1909.) Confirmed P.M.
Eliz. Charlton (née Lowes), aged 29 years. (S.C.D.—died 1926.)

The descendants of this family, nearly thirty in number, are at present being investigated with special regard to gastric analysis and blood changes. Up to the time of writing, the four sons of Henry Watson have been examined; in two of them achlorhydria is present.

Similar investigations are being carried out in another family, in which two sisters have been affected: one died of pernicious anæmia six years ago, whereas the other is now under treatment for subacute combined degeneration.

Onset.—As a rule the patients have been singularly free from previous illnesses. The onset was usually insidious (58 cases). In the three remaining cases, however, the disease began suddenly in the form of an attack of so-called "influenza" with fever and pains in the back and limbs. This was shortly followed by numbness and tingling in the hands and feet and weakness in the legs. A sudden onset was not necessarily associated with a rapid subsequent course.

In 39 cases (63·9 per cent.) the first symptoms were referable to the nervous system:—

Numbness and tingling in 15 cases; it is interesting that in two of these the patient stated that the first symptom was a tingling at the tips of the fingers or toes on flexing the head.

Weakness or stiffness of the legs in 17 cases; occasionally commencing unilaterally (3 cases).

Pains in the back or limbs in 4 cases.

In 10 cases (16·4 per cent.) the earliest symptoms were referable to the alimentary tract. These consisted usually of indigestion and vomiting, and occasionally diarrhœa; in one instance the initial complaint was a sore tongue.

In 12 cases (19·7 per cent.) the first symptoms were attributable to anæmia. These comprised such complaints as pallor, general weakness, shortness of breath, and palpitation. Two of these cases deserve fuller description. Collier [3] states that no case has ever been reported in the literature in which a patient, already under observation for pernicious anæmia, has developed signs and symptoms of combined degeneration of the cord. Piney [20] appears to be of the same opinion. In this series it has occurred definitely in two instances.

Case 16.—S. M., aged 46, female, was admitted on April, 1927, with a three years' history of anæmia and general weakness. Vomiting had occurred during the past year. No numbness or tingling was present, and nothing abnormal was found in nervous system. Gait was not unsteady. Glossitis was present and some pyorrhœa. Blood-films were typical of pernicious anæmia. Red blood-cells numbered 2,370,000, and the colour index was above 1. The white blood-cells were 10,000 per c.mm. Wassermann test was negative. At this period the patient was an uncomplicated case of pernicious anæmia.

Under liver treatment she improved, and at the end of three months felt quite well (August, 1927). She then stopped taking liver because she had difficulty in digesting it in the hot weather, and thought that there was no need to continue with it. About four months after the cessation of liver diet she became much worse. Not only did her pallor return, but she began to complain of "pins and needles" in the extremities, and later became unsteady on her feet, so that she staggered as if drunk. The condition progressed, and finally she lost the use of her legs.

In May, 1928, the patient was re-admitted to hospital, having had no liver diet for ten months. On examination she was grossly anæmic, with a yellow skin. Glossitis was present. The spleen was not palpable. She complained of numbness and tingling in the extremities, of headaches, and was unable to stand. Knee and ankle jerks were present, but the plantar reflexes were not obtained. Some inco-ordination was present, and sensation was much blunted in the legs. Red blood-cells numbered 1,083,000, the hæmoglobin being 20 per cent.

Liver diet was recommenced, with a half-pound of cooked liver daily. The response was rapid, and the reticulocytes rose to 20 per cent. When discharged a month later the red blood-cell count had risen to 4,202,000 per c.mm. and the hæmoglobin to 50 per cent.

After leaving hospital she continued to take about one and three-quarter pounds of liver a week.

On December 6, 1928, she was re-examined. She has gradually improved, has gained in weight, and can now walk without the aid of a stick. The knee-jerks are present and the ankle-jerks absent. The plantar reflexes are doubtful. Co-ordination is good and Romberg's sign negative. There is slight impairment of joint sense, and vibration sense is deficient below the knees. Sensation to touch and pin-prick is normal. Red blood-cells number 3,510,000, hæmoglobin is 70 per cent. and the colour index 1. White cells are 6,000 per c.mm.

The course of events in this case may be divided into four stages :—

(1) A stage of pernicious anæmia without any symptoms or signs of involvement of the spinal cord.

(2) Rapid remission of the anæmia with liver treatment.

(3) Relapse of the disease following cessation of the liver diet, with the development of subacute combined degeneration of the cord.

(4) Gradual improvement of both blood and nervous phenomena after a further course of liver treatment.

The following case is another interesting example :—

G. R., aged 42, male, was admitted in May, 1925, as a case of pernicious anæmia. He complained of weakness and pallor and of vomiting and diarrhœa. The tongue was clean, with doubtful glossitis, and he was markedly anæmic. The spleen was not palpable. There was total achlorhydria. No abnormal signs were found in the nervous system. Red blood-cells numbered 760,000 per c.mm., and the film was typical. He then had a remission and was well for a few months.

March, 1926.—Readmitted with relapse. He was grossly anæmic, with yellow colour, and complained of vomiting and diarrhœa. Signs of spinal involvement were now beginning to appear. The knee and ankle jerks were exaggerated, and ankle clonus was present. The plantar reflexes were "flexor." There was inco-ordination of the legs. Red blood-cells numbered 688,000, hæmoglobin was 16 per cent., and the colour index 1·3.

After a blood-transfusion his red cell count rose to 3,180,000, and he was discharged.

September 1926, he was again admitted.

After leaving the hospital in April, he had returned to work and had been fairly well until four weeks ago. Vomiting and diarrhœa had recommenced and weakness of the legs developed. His feet were numb with "cotton-wool" feeling and some loss of sensation. There was gross inco-ordination of arms and legs, and Romberg's sign was very marked. The knee and ankle jerks were active; the abdominal reflexes were absent, and the plantar reflexes "flexor." He was very pale with a yellow colour, and was extremely ill. His temperature was 104°, and the pulse 130 per minute. Red blood-cells numbered 950,000 and the white cells 5,600.

He died a week after admission. On autopsy, in addition to the usual changes found in cases of pernicious anæmia, there was extensive degeneration of the posterior columns of the cord.

Symptoms and Signs.

These will be considered under the headings of nervous system, alimentary tract, and blood.

Nervous system.—Numbness and tingling, or "pins and needles" in the extremities, generally of "glove and stocking" distribution, was invariably present.

In addition, various other dysæsthesias were noted, such as girdle sensation and pains in the back and limbs, and a common complaint was that objects felt cold to the skin.

Inco-ordination and ataxia of the lower limbs were present in all cases in which there was sufficient power for these signs to be elicited.

Vibration sense in the tibiæ was impaired or absent whenever noted.

Joint sense in the big toes was also absent or impaired whenever noted, with one exception (Case 5).

Anæsthesia to touch and pin-prick of varying degree was present in the extremities in a fair proportion of cases. In 12 cases the anæsthesia was gross in degree, and in two of these it extended up as far as the waist.

Astereognosis was a feature in 8 cases.

Reflexes: The knee-jerks were absent in 12 cases, and the ankle-jerks in 11 cases. More frequently (27 cases) the deep reflexes were exaggerated even in the very advanced cases just prior to death. The plantar responses were extensor in type in 41 cases. In three fatal cases the plantar responses remained flexor throughout. In one of these an autopsy was performed, and showed involvement of the posterior columns of the cord only.

Athetoid movements occurred in one instance (Case 7). These were slow rigid movements of the hands, which continued incessantly throughout the course of the disease. It is interesting that in this case stimulation of certain areas in the lower limbs produced diffuse pain of thalamic type.

Ocular manifestations occurred in several instances. Some degree of optic atrophy of the primary type was noted in three cases, the diagnosis being made on ophthalmoscopic evidence; nystagmoid movements were present in six and diplopia in two cases, in one of which it was associated with a paralysis of the fourth nerve.

Mental disturbances were present in three cases. In one there was a marked indifference to surroundings, almost amounting to stupor. In the second (Case 21) delusions of persecution were present, whilst the third (Case 26) suffered from delusional insanity, which necessitated certification.

Disturbances of micturition were encountered in 26 cases. These included difficulty (12 cases), incontinence (11 cases), retention (2 cases), and precipitancy (1 case). It is worthy of note that in all except two of these cases the trouble was accompanied by other evidence of pyramidal involvement (i.e., extensor plantar reflexes).

Alimentary tract.—Symptoms or signs indicating involvement of the alimentary canal were invariably present.

Teeth: No case was encountered with sound teeth. There was either definite pyorrhœa present, or else all or most of the teeth had been extracted. In some cases this had been carried out fifteen to twenty years prior to the onset of the disease.

Hunterian glossitis was noted in 29 cases; of these 18 complained of soreness of the tongue.

Gastro-intestinal symptoms were a common feature. Indigestion was noted in 22 instances; this usually took the form of discomfort after meals, with or without actual pain. Vomiting occurred in 11 of these cases. Diarrhœa was a feature in 3 cases.

Achlorhydria was found in every case in which a fractional test meal was performed (44 out of 61).

Blood.—In every case except six, a definite degree of anæmia (viz., below 4 millions per c.mm.) was present when the patients first came under observation. The average count for all the cases was 2·59 millions, the lowest being 680,000 and the highest 5·6 millions.

It is interesting to note that the three cases who survived for more than two years without liver treatment all had comparatively high counts—viz., 5·6, 4·45, and 3·9 millions per c.mm. respectively.

The colour index was usually, but not invariably, above unity.

The blood-films as a rule were sufficiently typical of pernicious anæmia to be of great value in diagnosis.

When the degree of anæmia is not marked, special methods may be necessary to detect the presence of macrocytosis. These include such means as the Price-Jones curve and the diffraction method.

Yellow discoloration of the skin was present in the cases in which anæmia was at all marked.

The spleen was sufficiently enlarged to be palpable in seven cases.

II.—EFFECTS OF LIVER THERAPY.

A study of the literature shows that opinions vary as to the effects of liver treatment on subacute combined degeneration. Thus, Minot and Murphy [15] describe the effects of this form of treatment in thirty-one cases of pernicious anæmia with prominent symptoms or signs of degeneration of the spinal cord. In nearly all instances numbness and tingling in the extremities had either disappeared or had been much reduced; co-ordination had improved in many, and vibration sense in some cases. Changes in reflexes had remained unaltered. They appear to attribute the improvement to an increase of muscular strength, secondary to the continuous high level of the number of red blood-cells and attach importance to appropriate re-educational exercises.

Koessler and Maurer [10] report two cases, and Bubert [1] and Mason [12] each describe a single case, in which marked improvement in the nervous phenomena occurred on liver diet. Sturgis, Isaacs and Smith [22] found that "improvement in the signs and symptoms of combined posterior and lateral sclerosis of the spinal cord did not parallel the regeneration of the blood, although slow improvement in the neurological condition has frequently followed the combined use of liver extract and physiotherapy."

Wyman Richardson [21] describes fourteen cases with ataxia, of whom eight showed considerable improvement, and four moderate improvement.

On the other hand, Cohen [2] reports a case in which, while there was a distinct general improvement on liver diet, the nervous condition progressed.

Middleton [14] states, "In the majority of cases certain of the lesser evidences of cord involvement, as paræsthesias, weakness and unsteadiness of gait, have been reported improved or relieved; but it is an unusual experience, and scarcely to be anticipated from the underlying pathologic process, that grave cord signs will abate under any form of treatment."

Similarly Ordway and Gorham [19] are of the opinion that advanced cord changes persist almost without exception.

Fried [5], after describing the pathological changes in the cord, concludes: "The serious character of the lesion of the spinal cord in pernicious anæmia, and the peculiarities of tissue repair in the central nervous system render impossible a cure in the spinal cord symptoms under the influence of liver diet. In view of the nature of the lesion, likewise, one may not expect great improvement in the nervous symptoms even though the anæmia has disappeared, and it is remarkable that any functional improvement at all should occur."

Thirty of this series of sixty-one cases have been treated by feeding on liver. On the whole, the results have been very promising. Where the liver régime has been adequately carried out improvement has occurred, not only in the general condition but also in the nervous phenomena. In a few cases, however, in spite of intensive liver treatment death has occurred, due in most instances to the supervention of some serious complication.

On the other hand, those cases who have discontinued the liver, or have taken it in very small quantities, have become worse or shown but little improvement. Some have improved temporarily and then relapsed when the liver was stopped. The large majority of the cases not treated by liver have died, and in the remainder the disease has taken its usual downward course.

These results are shown in tabular form below:—

	Liver	No liver
Improved	17	0
Not improved, or worse	8	3
Deaths	5	28
Total	30	31

The duration of the disease in these two groups is discussed elsewhere in this paper.

Of the seventeen patients who improved (Cases 1 to 17), eight (Cases 1 to 8) are back at work, and nine, although not working, are much better and able to get about. These patients have been on liver treatment for a period varying from nine to twenty-seven months, the average period being sixteen months. They are all taking 1 to 3 lb. of liver per week.

Of the eight patients (Cases 18 to 25) in whom the symptoms are unchanged, on investigation seven proved to have stopped the liver, or to be taking only small amounts, e.g., ½ to ⅓ lb. per week. In the eighth case (Case 18) there was a septic condition of the urinary tract.

Five cases (Cases 26 to 30) died in spite of liver treatment. In at least four of these serious complications were present, and the amount of liver taken was small.

Of thirty-one cases not treated by liver, twenty-eight have died, and three, though still alive, are worse. None has improved. Included in this "non-liver" series are two cases who had had liver or liver extract in insignificant amounts. One was admitted in a moribund and semi-conscious condition, and although able to take a small quantity of extract on one occasion, died within forty-eight hours. On autopsy, in addition to the usual findings, marked pyelonephritis was present.

The other case was also admitted *in extremis*. There being no extract available at the time, ordinary cooked liver was administered. He only managed to take it in very small quantities on two or three occasions and died within a week of admission.

On account of the grossly inadequate quantities of liver taken in these two cases, it has not been considered justifiable to include them amongst those treated with liver.

The liver-treated cases will now be considered in detail, describing first some examples of improved cases, then those who remained *in statu quo*, and lastly the deaths.

Improved Cases.

Case 1.—G. B., aged 46, male, foreman plumber, was admitted January 9, 1928.

History.—Eighteen months before admission he had an attack of "influenza" which was followed immediately by symptoms of subacute combined degeneration, including numbness and tingling in the hands and feet, and shooting pains in the legs. The tongue was sore at times; his teeth had been extracted. Pallor became noticeable. For eighteen months the numbness increased and he became progressively weaker.

Four months ago walking became difficult, and this trouble increased so that for the two weeks prior to coming into hospital he was unable to walk at all. No previous illnesses and nothing of note in the family history.

Condition before liver treatment.—Marked pallor. Spleen and liver were not palpable. Complete achlorhydria found on fractional test meal. Lower limbs were weak with exaggerated knee-jerks and ankle-jerks, and extensor plantar reflexes. Vibration sense was absent below the knees. There was marked loss of muscle and joint sense, with gross inco-ordination, and Romberg's sign was present. Some impairment of sensation to touch and pin-prick was elicited. Blood-films were typical, and the red blood-cells numbered 2,130,000; hæmoglobin was 40 per cent. and the colour index 0·9. White blood-cells were 9,680 per c.mm.

He was given ½ to 1 lb. of liver daily, and the reticulocytes rose to 13 per cent. on the seventh day of treatment.

After three weeks the red blood-cells amounted to 4,760,000 and hæmoglobin 70 per cent.

There was some diarrhœa in the initial stages, but this soon passed off. He gained a stone in weight (weight now 8½ st.), but on discharge (March 3), he was still unsteady, and the nervous signs were unaltered.

After five months of liver treatment: On May 22 he returned for re-examination. Since leaving hospital he had been taking 1½ lb. of liver per week. A marked improvement was now manifest. His only complaint was some pain in the heels and toes on walking fast, and he expressed a desire to return to his work in the shipyards.

On examination: colour good and now weighed 10 st. 5½ lb. Knee-jerks and ankle-jerks were exaggerated and ankle clonus was present on the left side. The plantar reflexes were now flexor. Subjective and objective sensation was noted as normal. Muscle sense was normal and Romberg's sign negative. Vibration sense was now present in all bones, though still diminished in degree. Red blood-cells numbered 5,437,000 and hæmoglobin was 90 per cent. Achlorhydria was still present.

In June he commenced light work, and by August he was back at the job he held prior to his illness, namely foreman plumber in the shipyards.

After eleven months of liver treatment (i.e., on December 6) the patient was again examined. He had been working for six months now, and felt perfectly well except for an occasional sensation of stiffness in the calves. He continues to take 2 lb. of liver weekly (usually stewed for one and a half to two hours).

Nervous system.—Knee-jerks and ankle-jerks were much exaggerated and patellar clonus was present but no ankle clonus. The plantar reflexes were flexor. Co-ordination was good and Romberg's sign negative. Joint sense was only slightly impaired and there was no anæsthesia to touch or pin-prick. Vibration sense was normal. Red blood-cells numbered 5,060,000, hæmoglobin was 100 per cent. and colour index 1. White blood-cells were 6,000 per c.mm.

After sixteen months (May 6): Apart from some slight numbness of the feet at times, he remains quite fit and is working some fourteen hours a day in the shipyards. He is now taking 1½ lb. of liver per week. Another fractional test meal was performed and still failed to reveal the presence of free hydrochloric acid.

The improvement in this case is particularly striking. As a foreman plumber he works in many parts of a ship during its construction, an occupation requiring perfect co-ordination of movements and a delicate sense of balance. Not only is he practically free from symptoms, but the signs of involvement of the cord have almost disappeared. Particularly noteworthy in this connection is the change of the plantar reflexes from extensor to the flexor type.

Case 2.—T. F., aged 55, male, miner, was admitted February 10, 1928.

History.—Trouble commenced with pain in stomach eight months before admission, and soon after he had difficulty in walking and began to get pale. Later he complained of "pins and needles" in hands and feet. A month before coming into hospital he was extremely unsteady and could not walk or stand. His tongue was never sore.

He had had no previous illness and his family history was unimportant.

Condition before treatment.—Very pale. Slight glossitis at edges of tongue. Knee and ankle jerks were exaggerated, and ankle clonus was present. Plantar reflexes: right extensor, left doubtful. Romberg's sign was very marked and he was unable to stand without assistance.

Red blood-cells numbered 1,100,000, and hæmoglobin was 34 per cent. The film was typical of pernicious anæmia.

A fractional test meal revealed achlorhydria.

Liver therapy: Half a pound of liver was administered and has been continued since leaving hospital on March 13. He started work eight months later.

After nine and a half months of liver treatment (i.e., on November 28), patient was again examined. He is now working eight and three-quarter hours a day as a miner, and feels only slight tiredness after standing six hours. He has now no numbness or tingling and only some slight temporary paræsthesia in the feet when he gets up in the morning. He has gained a stone and a half in weight.

His colour and general condition is excellent. Knee-jerks and ankle-jerks active and equal. Plantar reflexes: left flexor, right doubtful—probably extensor. Vibration sense present in all bones, but slightly diminished in right leg. Sensation to touch and pin-prick normal. Co-ordination normal. Red blood-cells numbered 5,400,000 and hæmoglobin was 100 per cent.

After thirteen months (i.e., on March 30). Now taking 1¾ lb. of liver per week. Improvement is maintained and he has not missed any work. He complains of numbness and tingling at times, especially towards the end of the day's work.

This is another excellent example of subacute combined degeneration treated by liver, in which nervous symptoms have so far regressed as to enable him to earn a living by manual labour.

Case 9.—J. T., aged 39, male, a fitter in shipyards, was admitted on May 12, 1928.

History.—Worked regularly as a fitter until three months before admission, when he began to complain of shortness of breath and palpitation, with indigestion and flatulence, some general weakness and slight cough.

One month later he complained of "pins and needles" in the hands and feet, and noticed that he was very pale with a yellow tinge. One month before admission he was unable to walk. Tongue had not been sore.

Previous history.—Always sallow, but in good health and a regular worker. Operation for hæmorrhoids, 1915. Bilious attacks since boyhood at intervals of three to four months. People used to remark that he often looked jaundiced.

Family history.—Father aged 75 suffers from diabetes. Mother aged 71 is healthy. Three brothers all healthy. Three sisters, one of whom was operated upon for goitre. Five nephews and nieces, none of whom are anæmic. Four children; one suffers from asthma.

Condition before treatment.—Unable to stand, but can move legs in bed. Gross inco-ordination. Complete analgesia, touch diminished and some loss to heat and cold in legs. Marked numbness and tingling in hands and feet. Cannot write. Astereognosis marked. Knee-jerks and ankle-jerks present. Plantar reflexes doubtful on both sides. Skin yellow, mucous membranes very pale. Hunterian glossitis present. Pyorrhœa present. Spleen and liver not enlarged. Apex of heart in sixth space in nipple line; systolic hæmic murmurs at apex and base. Blood-pressure 130/90. Fractional test meal showed complete achlorhydria. Van den Bergh test gave an indirect positive result and the Wassermann reaction was negative. Red blood-cells numbered 1,200,000; the hæmoglobin was 22 per cent. and the colour index 0·9.

Liver therapy.—From May 19 onwards, liver extract (Oxo) was administered twice a day; after three weeks this was discontinued in favour of cooked liver, of which half a pound was given daily. On the third day of treatment he experienced some difficulty of micturition, without change in the nervous phenomena. A reticulocyte crisis of 17 per cent. occurred and by the fourteenth day the red cells numbered 2·4 millions. Co-ordination and power in the legs and arms were improved and he was now able to turn easily in bed, could shave himself and write. Numbness and tingling had greatly diminished in the legs, but had increased in the hands. The deep reflexes were more easily elicited, and touch and pain sense had returned except in a small area on the back of the thighs.

After seven weeks of liver therapy he attempted to stand but failed, owing to pain and weakness. Tingling in the feet was reduced to "a rough feeling," but there was still some numbness of the back of the thighs. Co-ordination exercises for the feet were commenced. Red cells now numbered 4·1 millions.

By the ninth week he was able to stand without assistance after being steadied. Numbness and slight anæsthesia were still present on the back of the thighs. The knee- and ankle-jerks were active and the plantar reflexes extensor in type. The red cell count reached 7·1 millions, and hæmic murmurs had disappeared. He was discharged a month later.

After six and a-half months of liver treatment, i.e., extract for twenty days, 3½ lb. of cooked liver per week for three and a half months, and 1½ lb. per week since, the patient was re-examined (December 6, 1928). Now able to walk two miles a day with ease; uses a stick, but can do without it; slight difficulty in the dark. Does not now complain of shortness of breath: his appetite is good. Only complaint now is a sore patch below left costal margin; this has no relation to food. His tongue, which is not sore, shows slight glossitis at edges. No numbness or tingling, only a "rough" feeling at times. Occasional stiffness in lower parts of calves. Micturition normal.

Nervous system.—Knee-jerks active and equal; ankle-jerks absent. Plantars extensor in type. Abdominal reflexes present. Co-ordination good. No ataxia. Appreciation of vibration absent in all bones below knees. Joint sense absent in joints of toes, but present in the larger joints. Sensation to pain and touch good. Writing very good. No astereognosis. Red blood-cells numbered 5,000,000 and hæmoglobin was 90 per cent. White blood-cells were 11,000 per c.mm. Colour index was 0·9.

After twelve months (i.e., May, 1929): He has been taking 1½ lb. of liver per week, and is still improving. Slight tingling is present in the feet, but he is quite steady and can walk long distances without the aid of a stick. He is looking for work. Vibration sense has returned although joint sense is still absent in big toes. The deep reflexes are unchanged, but the plantar reflexes have become flexor.

It is interesting to note the rapidity of the improvement in this case. The first definite change in the nervous phenomena, both subjective and objective, was noticed twelve days after the commencement of liver treatment. This rapid improvement may in part be due to the early stage at which liver therapy was commenced, namely, three months after the onset of the disease. This is another instance in which the plantar reflexes, formerly extensor in type, have become flexor.

Case 10.—J. O., aged 49, female, married, was admitted on September 13, 1927.

History.—The trouble started with pain in the back in August, 1926. Weakness of the legs was noticed in December of that year, with numbness and tingling in extremities. Within a few weeks she was unable to walk at all, and took to bed.

While she was in hospital for a month (February 17 to March 17, 1927), the plantar responses were noted as both extensor. The Wassermann reaction was negative. She was discharged unchanged and remained in bed with almost complete paralysis of the legs, which were insensitive up to the hips.

Condition before liver treatment.—Re-admitted September 13, 1927, with complete inability to walk or move her legs, but she had some voluntary power in the individual muscles and could move her toes. Much numbness in hands and legs. Difficulty with micturition. Knee-jerks very sluggish, ankle-jerks absent, and plantar reflexes extensor. Joint sense was grossly deficient. She was anæmic and glossitis was definite. Fractional test meal showed complete achlorhydria. Red blood-cells numbered 2,120,000.

Liver therapy.—Half a pound of liver was given daily, and when discharged on October 28, 1927, she could move her legs well. She continued to take ½ lb. of liver each day for a year, and has taken 2 lb. a week since.

After fourteen months: On December 3, 1928, after fourteen months of liver treatment, patient was re-examined. She had improved immensely and could now walk with the aid of a stick. Colour and general condition were excellent. Pupils were sluggish and the optic discs normal. Legs spastic. The knee-jerks were present, ankle-jerks absent, and the plantar reflexes extensor. Vibration sense normal, but there was slight blunting of sensation to touch and pin-prick. Co-ordination was poor, and joint sense impaired in legs. Power in legs was good and she could walk with the aid of a stick.

Red blood-cells numbered 5,170,000, hæmoglobin was 100 per cent. and the colour index 1.

After nineteen months there is still further improvement and she can walk better. There are no further changes in the nervous system, except that there is less spasticity and more power in the legs. The condition of the blood remains satisfactory.

This case is noteworthy on account of the advanced stage of the disease at which liver treatment was commenced; she had then almost complete paraplegia. She has improved steadily on liver diet and continues to do so.

Unimproved Cases.

These cases will now be described and analysed with a view to ascertaining the possible reasons for the failure of liver treatment.

Case 18.—M. W., aged 61, female. She took 1 to 3 lb. of liver per week for five months; but only ¾ lb. per week for the last twelve months. She improved for a while, but later regressed and is now bedridden. Urine contains much pus and albumin. Incontinence of urine. Red cell count numbered 4·2 millions.

Case 19.—R. R., aged 45, male. He took 2 lb. of liver per week for three months, but none for past seven months. He is now bedridden with incontinence of urine. The red cell count is 4·1 millions.

Case 20.—R. L., aged 45, male: 2½ to 3 lb. of liver per week was administered for fourteen months, but none for the last six weeks. He improved in general condition at first, but rapidly went downhill after stopping liver. Red cell count was 2·2 millions. Plantar responses are now extensor. There is marked pyorrhœa and the urine contains a few pus cells and red corpuscles, and a minute trace of albumin. He is now bedridden, although during the past few months some improvement has occurred in hospital while on full dosage of liver. The red cells number 4·2 millions.

Case 21.—D. A., aged 44, female; ¼ lb. of liver a day was taken for three months, but none for past twelve months. She is still bedridden. Red cells number 2·4 millions.

Case 22.—M. M., aged 54, female; ¼ to ½ lb. of liver per week for twelve months, but none for past two months. She is no longer bedridden, but is still unable to stand and has very little power in her legs. Extensor spasms have ceased and numbness and tingling have diminished. The red cells number 5·2 millions.

Slight improvement has occurred, but as she is still paralysed the case is included amongst those who have remained *in statu quo.*

Case 23.—S. G., aged 44, female, took ½ lb. of liver per week for some months, but none for last few months. She is still bedridden and although her general condition has improved, the nervous symptoms are worse, the legs being weaker and more spastic; flexor spasms are marked. The red cells number 3·2 millions per c.mm.

Case 24.—E. N., aged 42, female, took ½ lb. of liver per week for six weeks, ½ lb. per week for a short time irregularly, and none for the past few months. She improved markedly at first but relapsed after discontinuing the liver. Red cells numbered 3·7 millions. Recently this patient has been re-examined; she has been taking ¼ lb. liver per day for the past four months, but has not improved. Pyorrhœa is present. Urine contains nothing abnormal. Red cells number 3·2 millions. The spleen is enlarged.

Case 25.—J. A., aged 50, male, took ¼ lb. liver per week for some months, but none for past few months. He improved at first, but has become worse lately. He read of liver treatment in the press, but was not ordered it by doctor. Has lately developed carcinoma of rectum for which he has been operated upon.

From a consideration of the above reports, it will be seen that a constant feature in these cases is the fact that small and irregular amounts of liver were taken. The presence in many of the cases of dental and urinary sepsis is also a notable feature. The influence of these factors on prognosis will be discussed later.

Five cases died in spite of liver treatment. These will now be described in more detail.

Case 26.—R. T., aged 41, male, miner, was admitted on October 3, 1927, as an advanced case of combined degeneration of the cord, with a blood-picture typical of pernicious anæmia. There had been a fifteen months' history of numbness and tingling, with difficulty in walking.

Half a pound of liver was administered daily. On the tenth day the red cell count had increased to 5,570,000, and the reticulocytes to 7 per cent. Some days later he started to cough up purulent sputum, which contained Gram-positive diplococci, but no tubercle bacilli. Moist sounds at bases of lungs, but no impaired resonance. Looked ill. Temperature 101°. Pulse 132. Respirations 24. He soon showed some improvement, and was able to walk before leaving the hospital. Shortly after returning home, although taking ½ lb. of liver a day, he started to get worse. He became pale and yellow, and the delusions (from which, according to his wife, he had been suffering for twelve months) became more intense. Nine weeks after leaving the hospital he was removed to a mental institution, where he died six weeks later. No liver was administered during the latter period.

We cannot account for the fatal termination in this case, unless it was accelerated by the marked and long-standing delusional insanity, and perhaps by his pulmonary condition, the nature of which had never been definitely determined.

Case 27.—K. L., aged 53, female, was admitted on September 24, 1928, as a well-marked case of combined degeneration, having complained of numbness and tingling in the hands and feet for eighteen months, and weakness in the legs for the past four months.

She was given ½ lb. of cooked liver per day; this evoked a reticulocyte crisis, and improvement in her general condition followed. A month later she developed gangrene of the left foot. Severe general convulsions preceded her death, which took place a fortnight after the onset of the gangrene, and during which time the liver had been discontinued.

Death in this case was presumably due to the gangrene. It is not possible to state definitely whether liver administration was the cause of the arterial thrombosis. In this connection, it is noteworthy that two cases of venous thrombosis during liver treatment have come under the notice of the writers.

Case 28.—J. E., aged 65, male, admitted on January 5, 1928, as a very advanced case of combined degeneration, with marked Addisonian anæmia and sphincter trouble. The urine contained albumin and pus.

Administration of B.D.H. liver extract (8 grm. daily; equivalent of ½ lb. of liver) was commenced on January 9. This was continued for six days, and as no improvement occurred, the dose was increased to 16 grm. daily for a further eight days. This treatment had no effect on his blood, not even evoking a reticulocyte crisis. Bed sores developed, the urinary symptoms became worse, and the nervous phenomena progressed, the recti abdominales becoming paralysed.

He died twenty-four days after admission, having been treated with liver extract for fourteen days. During this period he had a total of 88 grm., which is the equivalent of 11 lb. of liver.

On post-mortem examination, apart from evidences of pernicious anæmia and of subacute combined degeneration of the cord, advanced double chronic pyelonephritis and chronic cystitis were found.

The immediate cause of death in this case was apparently the pyelonephritis. The presence of this condition may also have been responsible for the fact that on intensive liver therapy the blood condition did not improve, and that no reticulocyte crisis occurred.

Case 29.—J. E., aged 59, admitted on June 21, 1927, having complained of loss of power in legs with numbness and tingling in the hands and feet for six months. He became increasingly helpless and developed pyramidal signs and sphincter trouble, which was followed by marked infection of the urinary tract.

Liver diet was advised, but he only managed to take very small quantities at irregular intervals for a short period. Death took place six months after leaving hospital.

In this case the question of the influence of liver diet does not arise to any extent, as, although taken for some months, the amounts were grossly inadequate. The fatal termination, however, was due to the long-standing septic infection of the urinary tract.

Case 30.—G. S., aged 51, male, admitted on August 15, 1928. In January, 1928, complained of pallor and weakness and difficulty in walking, which progressed rapidly.

Small quantities (½ lb. per week) of liver were started shortly afterwards, and continued for three months, during which time there was no change.

In May, administration of liver extract (Boots') was commenced, the dose being one tube per day (the equivalent of ½ lb. of liver). He soon improved in colour, increased in weight, and was able to walk for short distances unaided. A month before admission, however, he suddenly lost the use of his legs completely. In hospital, although the state of his blood was now satisfactory, the nervous system exhibited the picture of an advanced case of subacute combined degeneration of the cord, complicated by sphincter trouble and a bad cough. He was discharged after a week and died a month later, having had no liver during the last month.

With the above patient there appear to have been no serious complications which might have rendered liver therapy unavailing, and thus the failure of the treatment in this case cannot be accounted for.

An analysis of the effects of liver therapy in the seventeen improved cases – and a comparison of their condition before and after treatment.

From what has been said already, it is clear that only by a study of the seventeen improved cases is it possible to determine the effects of a full and prolonged course of liver diet on the signs and symptoms of subacute combined degeneration.

The duration of the disease before treatment was commenced in these cases varied from three months to two years—the average duration being 13·7 months.

The duration of liver treatment varied from eight to twenty-eight months, the average period being 16·6 months.

The condition of these cases before and after treatment will now be considered under the headings of blood, alimentary tract and nervous system, followed by general remarks.

Blood.—Considerable anæmia was present in all the seventeen cases. The lowest red cell count was 1·1 millions per c.mm. and the highest 3·6 millions; the average count being 2·13 millions per c.mm.

(In one instance, Case 15, the red-cell count on admission had been noted as 4·1 millions in our previous paper; it has since been ascertained that this patient had had liver previously at home, and that he had been very anæmic before this.)

As a result of liver treatment, the anæmia disappeared within one to three months. At present, after an average period of 16·6 months of liver diet, the mean red cell count is 4·9 millions.

In every case in which the blood was stained by vital methods during the initial stages of liver administration, a reticulocyte crisis was observed.

No enlargement of the spleen can now be detected in the two cases in which it was formerly palpable.

Alimentary tract.—Soreness of the tongue (six cases) cleared up very rapidly, usually within a few days of commencing the liver diet.

Hunterian glossitis (thirteen cases) was still recognizable after the long periods of liver treatment, but no sign of acute inflammation persisted in any of the cases.

Indigestion with gastric pain (nine cases) and vomiting (four cases) cleared up in a remarkable manner very soon after the commencement of the diet. After an average period of sixteen months' treatment indigestion is present in only two cases, and in these it is not severe.

Transient diarrhœa occasionally occurred during the initial stages of the liver administration.

Many of the patients now complain of constipation, which they attribute, rightly or wrongly, to the liver diet.

Achlorhydria.—Further fractional test meals have been performed in five cases after an average period of 16·7 months of liver treatment. There is still complete achlorhydria in each case.

This confirms the reports of Heath [6], of Minot, Murphy and Stetson [17], and of other observers. However, it is interesting to note that Heeres [7] reports a case in which there was return of free hydrochloric acid in the stomach contents after a period of liver treatment extending over nine months.

NERVOUS SYSTEM.

Seventeen cases have already been described which illustrate the beneficial effects of liver diet upon the nervous phenomena of subacute combined degeneration. It now remains to analyse the effects of the treatment upon individual symptoms and signs in these cases.

Subjective sensations.—Numbness and tingling in the extremities (present in every case of the seventeen) disappeared completely in ten cases, and remained to only a very slight extent in the remainder. A transient increase occurred in a few cases in the early stages (see Case 9).

Lightning pains, girdle sensations and cramps (present in a few cases) cleared up completely.

Incoordination and ataxia, with loss of muscle sense in the lower (and occasionally upper) limbs, which were present in every case where sufficient power remained for them to be elicited, and were usually gross, improved considerably in all cases, and in ten cleared up entirely.

Objective sensory loss.—Sensibility to vibration sense was absent or impaired in the tibiæ in every case where it was recorded. It is now present normally in ten of the cases, absent in four, impaired in one, while in two it was not noted.

Joint sense has returned in six of ten cases where it was noted as having been absent.

Cutaneous sensibility to touch and pin-prick, noted as lost or impaired to varying degrees in twelve cases, was found to have become normal in eight of these. In the remaining four, there was but slight blunting of sensibility in small areas of the lower extremity.

Astereognosis, which was noted as being present in two cases, has disappeared completely in one case and partially in the other.

Reflexes.—The knee-jerks were absent in two cases, and exaggerated in the other fifteen. They remain unchanged.

The ankle-jerks were absent in four instances and have not returned. In the remaining thirteen cases these reflexes were exaggerated, and in eleven they still remain so. In the other two cases the ankle-jerks have since disappeared.

Extensor plantar responses, present in nine instances, have changed to flexor type in five cases (Cases 1, 9, 11, 12 and 15). In three of these double extensor responses have become both flexor, and in the other two the change involves one foot only.

Disturbances of micturition.—Either difficulty or incontinence was present in seven cases. In six the trouble has disappeared altogether, whereas the seventh complains of slight difficulty at times.

* * * * *

Before treatment ten of the cases were bedridden, while the remaining seven had such great difficulty in walking that they were confined to the house.

At the present time eight of them are working; three are miners, while the others are respectively a master plumber in the shipyards, a caretaker, a watchman, a clerk and a housewife.

Three further cases are ready for light employment, while the remaining six, although not yet capable of returning to work, are much better and able to get about.

Progress under liver treatment.—It is interesting to consider the order in which various signs and symptoms are influenced by liver diet.

Improvement in the blood, in the patient's general condition, and in the tongue and gastric symptoms occurs early, and is similar to that which takes place in pernicious anæmia.

As a rule, there is but little apparent improvement in the nervous phenomena during the first two or three months of liver diet. Case 9, however, is an interesting exception to this rule, as improvement in subjective sensations, co-ordination and power occurred within a few weeks, while the red cell count was still about 2,000,000 per c.mm.

Improvement in subjective symptoms and in the ataxia usually occurs first. The return of power is gradual and progressive. Alterations in objective signs only become evident later. The extensor plantar responses may not disappear for long periods, e.g., about twelve months in Case 9, ten months in Case 11, six months in Case 12, five months in Cases 1 and 15. In three other cases the plantar reflexes remain extensor type even after a period of one and a half to two years.

Vibration sense and joint sense may be very late in reappearing. In Case 9, after a year on liver diet, although the plantar reflexes are now flexor in type, and there is marked general improvement, vibration sense has only recently returned, and joint sense in the big toes is still absent.

PROGNOSIS.

Duration of disease.—Prior to the introduction of liver therapy, subacute combined degeneration was always regarded as a progressive and fatal disease. It is interesting to compare the duration of the condition in the "liver" and "non-liver" groups of this series. Of the 31 cases not treated by liver diet, only 3 are still alive, having suffered from the disease for periods of 2·1, 3·7, and 6 years respectively. The remaining 28 were dead within an average period of 14·6 months from the onset of the disease.

On the other hand, of the 30 liver-treated cases, although 5 died, the other 25 are still living after an average period of thirty-one months.

Factors influencing the response to liver.—The five fatal cases have already been discussed. Except in Case 30, the fatal result was due to serious complications, i.e., chronic pyelonephritis (two cases), gangrene and delusional insanity. These cases can scarcely be regarded as evidence against the efficiency of liver therapy in subacute combined degeneration. Insufficient evidence is available in the fifth case to account for the failure to respond to liver.

From a description of the unimproved cases, it will be seen that their failure to respond may be attributed to insufficient liver, cessation of the liver diet, sepsis, especially urinary or dental, or to a combination of these factors.

On the other hand, the seventeen improved cases have all had a full and prolonged course of liver treatment, (except Case 6, who recovered on as little as ½ lb. a week for seventeen months). In addition, no septic complications were present.

It is thus clear that the response to liver is dependent upon the dosage of liver and the duration of treatment, the stage of the disease at which treatment is commenced, and the presence or absence of sepsis. These factors will now be considered in detail.

The dosage of liver and the duration of treatment.—The best results have been obtained by an intensive course (3½ to 4 lb. a week) for six to eight weeks, followed by 1½ to 2 lb. of liver per week indefinitely. When such large quantities cannot be taken, the equivalent in liver extract may be substituted for all or part of this amount. The extract appears to be less efficient than whole liver.

Apart from cooked liver, or liver extract, the patients have taken their ordinary diet. The modifications concerning fruit and vegetables, restriction of fats, &c., as set out in the original diet recommended by Minot and Murphy [16], have not been made.

It is interesting to note that one patient (Case 5) had not been ordered liver, but nevertheless had improved immensely. On interrogation it was found that he had been taking ¼ to ½ lb. of liver, together with ½ lb. of kidney per week for long periods as part of his ordinary diet.

As a rule the appetite returns and digestive symptoms disappear, so that the patients exhibit little difficulty in taking the large amounts of liver. In other cases, however, the patient has tired of the liver and stopped taking it, with serious results.

We find that the minimum amount of liver required to maintain the blood-count at a normal level is not as a rule the optimum required for improvement in the nervous phenomena. In others words, the amount of liver required in subacute combined degeneration is greater than that necessary in "pure" pernicious anæmia.

Stage of the disease at which treatment is commenced.—The response to liver is, as a rule, less rapid, and the amount of liver required is greater in cases where there is marked and prolonged pyramidal involvement and sphincter disturbances.

Presence or absence of sepsis.—When there is active sepsis, such as pyorrhœa or urinary infection, the improvement under liver treatment is retarded, and larger amounts are required.

Richardson [21] is inclined to connect the improvement in the nervous phenomena on liver diet with the maintenance of the red blood count at 4·5 to 5 millions. Other observers including Minot and Murphy [15] also attribute the beneficial effects chiefly to improvement in the general condition coincident with the disappearance of the anæmia.

There are several reasons why we do not agree with this view :—

(1) The spinal changes of subacute combined degeneration are not the result of a low red count, and may occur in the absence of anæmia.

(2) The red cell count may be high for long periods on moderate amounts of liver without any improvement in the nervous system.

(3) Improvement in nervous phenomena may commence when the red cell count is as low as 2 millions (see Case 9).

(4) Cessation or diminution of liver may be followed by a relapse of the anæmia without any change in the nervous symptoms and signs. (This has recently occurred in two cases in this series, Cases 16 and 24.)

It appears that the beneficial effects of liver on the nervous system is a specific phenomenon, and not the result of the maintenance of the red cell count at a high level, or of improvement in the general condition.

ETIOLOGY.

Although the cause of subacute combined degeneration is, so far as we are aware, still unknown, recently acquired knowledge has shed new light on the nature of the disease.

The improvement which occurs on dietetic measures suggests a similarity to certain deficiency diseases, such as pellagra and lathyrism, in which involvement of the white matter also occurs. In addition, it is noteworthy that the histological changes in the cord in these diseases, bear a marked similarity to those found in subacute combined degeneration.

Bearing in mind the constancy of achlorhydria and the presence of a hereditary factor, it is possible that we are dealing with a deficiency disease occurring in persons with a certain constitutional diathesis.

In conclusion, it is evident that liver therapy has definitely beneficial effects on the symptoms and signs of subacute combined degeneration of the cord. It seems that, as with anæmia, so with the nervous phenomena, the remission brought about by liver therapy will only be maintained so long as the treatment is continued.

From clinical evidence, since all signs and symptoms of cord involvement may disappear, it would appear that the degenerative changes in the white matter in this disease are not necessarily of a permanent character.

We wish to thank Professor T. Beattie, Dr. W. E. Hume, Dr. Horsley Drummond, Dr. A. Parkin, Dr. George Hall, Dr. Wells Patterson, Dr. F. J. Nattrass, Dr. J. C. Spence, and Dr. O. W. Ogden for allowing us to use their cases for this investigation. We are especially grateful to Dr. F. J. Nattrass and Dr. J. C. Spence for their kindly help and criticism.

REFERENCES.

[1] Bubert, H. M. *Journ. Amer. Med. Assoc.*, 1928, **90**, 903.
[2] Cohen, A. E. *Ibid.*, 1928, **90**, 1787.
[3] Collier, J. "Textbook of the Practice of Medicine," 2nd Edition, 1926. Edited by F. W. Price.
[4] Dorst, S. E. *Amer. Journ. Med. Sci.*, 1926, **172**, 157.
[5] Fried, B. M. *Journ. Amer. Med. Assoc.*, 1929, **92**, 1260.
[6] Heath, E. H. *Ibid.*, 1928, **91**, 928.
[7] Heeres, P. A. *Nederlandsch. Tijdschr. v. Geneesk.*, 1928, **72**, 2163.
[8] Hurst, A. F. *Brit. Med. Journ.*, 1924, **1**, 93.
[9] Johannessohn, F. *Deutsch. Med. Wochenschr.*, 1925, **51**, 1953.
[10] Koessler, K. K., and Maurer, S. *Journ. Amer. Med. Assoc.*, 1927, **89**, 768.
[11] Liepelt, A. *Deutsch. Zeitschr. f. Nervenheilk.*, 1926, **90**, 201.
[12] Mason, E. H. *Journ. Amer. Med. Assoc.*, 1928, **90**, 1527.
[13] Meulengracht, E. *Amer. Journ. Med. Sci.*, 1925, **169**, 177.
[14] Middleton, W. S. *Journ. Amer. Med. Assoc.*, 1928, **91**, 857.
[15] Minot, G. R., and Murphy, W. P. *Ibid.*, 1927, **89**, 759.
[16] *Idem.*, *idem.* *Ibid.*, 1926, **87**, 470.
[17] Minot, G. R., Murphy, W. P., and Stetson, R. P. *Amer. Journ. Med. Sci.*, 1928, **175**, 581.
[18] Montgomery, E. W. *Canad. Med. Assoc. Journ.*, 1926, **16**, 244.
[19] Ordway, T., and Gorham, L. W. *Journ. Amer. Med. Assoc.*, 1928, **91**, 925.
[20] Piney, A. "Recent Advances in Hæmatology," London, 1927.
[21] Richardson, W. *New England Journ. Med.*, 1929, **200**, 540.
[22] Sturgis, C. C., Isaacs, R., and Smith, M. *Annal. Int. Med.*, 1928, **1**, 983.
[23] Tscherning, R. *Deutsch. Med. Wochenschr.*, 1926, **52**, 707.
[24] Ungley, C. C., and Suzman, M. M. *Newcastle Med. Journ.*, 1929, **9**, 67.

A STUDY OF THE HISTOPATHOLOGY OF TABES DORSALIS WITH SPECIAL REFERENCE TO RICHTER'S THEORY OF ITS PATHOGENESIS.

BY RUBY O. STERN, M.B.

(*From the Pathological Laboratory, National Hospital, London.*)

INTRODUCTION.

THE earliest conceptions of the histopathology of tabes dorsalis were based on the observations of Bourdon and Luys [2], who in 1861 described a sclerosis of the posterior columns and posterior roots as the result of a chronic inflammatory process, and of Charcot and Pierret [4], who ten years later described a systematic sclerosis of the posterior columns as characteristic of the disease. Pierret recognized the fact that certain parts of the posterior columns were involved in this sclerosis earlier than others, and he gave the name "bandelette externe"—or, as it is now called, "bandelette of Pierret"—to the external part of the posterior columns which appeared to be the first to degenerate. This observation was made on cases of tabes complicated by general paralysis, as it was hoped in these cases to find the early lesions of tabes. At this time Charcot and Pierret, Westphal [44], Strümpell [38], Flechsig [6], and other writers believed that the primary site of the lesion was in the spinal cord, but in 1879 Vulpian [43] suggested that a primary degeneration of the posterior columns could not lead to atrophy of the posterior roots, and he regarded the atrophy of the posterior roots as the primary lesion.

But it was not until 1894 that Obersteiner and Redlich [26], and shortly afterwards Nageotte [16], attempted to explain the lesions in the spinal cord by an inflammatory process beginning in the extra-medullary posterior roots. The new theories were rapidly adopted as they seemed to explain certain symptoms commonly met with in the disease which could not be explained by a slow primary degeneration of the posterior columns of the cord. Spielmeyer [36] more recently has tried to prove, with a certain amount of success, that some degeneration uninfluenced by extramedullary processes takes place in the posterior columns. The researches of Richter [29], by introducing a new theory, that of a specific granulomatous lesion, and those of Hassin [9], who has suggested yet another, the theory of retention of tissue fluids, have still further complicated the problem which has already aroused endless controversy: where is the initial lesion in tabes and what is its nature?

The difficulty is, of course, that cases of pure tabes do not often come to autopsy in the initial stages of the disease. If we are to ignore the cases of tabo-paresis, as Richter insists must be done, in order to eliminate possible confusion with pathological processes due to the paretic factor, then we are forced to wait, as Spielmeyer did, for chance to give us a case which does not survive the early symptoms.

If, on the other hand, we include cases of general paralysis with tabetic symptoms of recent onset, as Nageotte [17], and MacIntosh and Fildes [14] suggest, we encounter Richter's criticism [30] that we have introduced a new factor which either obscures the original tabetic lesion or makes the correct interpretation of it impossible.

But unless we are content to disregard practically all the work done on the histopathology of tabes prior to that of Richter, we must include, at least for purposes of comparison, cases of general paralysis with tabetic symptoms, for most of the early work was done on these cases. It is by no means certain how we are to assess the paretic factor. Jakob [11] particularly stressed this point. Why, he asked, should the changes found in the spinal cord and in the posterior roots in tabo-paresis be referred to the effect of the paretic process when they are not found in pure general paralysis?

In this study an attempt is made to examine three types of case: (1) Uncomplicated tabes in as early a stage as possible; (2) tabo-paresis; and (3) uncomplicated general paralysis; and to compare the observations made with a view to determining the significance of the changes found in their relation to the theories of the pathogenesis of tabes, more particularly to that of Richter.

THEORIES OF PATHOGENESIS OF TABES.

The work of Pierret, to which reference has already briefly been made, demonstrated that the earliest lesion inside the spinal cord was of the middle root-fibres, the central prolongations of exogenous fibres from the posterior nerve-roots. This distinctive selection of exogenous fibres did not preclude Pierret and his contemporaries from ascribing the pathological process to a primary intramedullary degeneration of the posterior roots, though they did not attempt to explain it. When

Obersteiner and Redlich [27] brought forward their meningeal theory of the vulnerability of the posterior roots at the point where they pass through the pia mater into the spinal cord owing to the normal diminution in myelin in this position, meningeal inflammation and hypertrophy alone were held to account for damage to the roots at this "locus minoris resistentiæ," causing secondary degeneration of the exogenous fibres in the posterior colums. But that other factors besides meningitis are necessary to produce tabetic lesions was recognized by Dejerine [5], who pointed out as the best proof of this that in individuals affected with syphilitic meningo-myelitis tabes is an exceedingly rare complication.

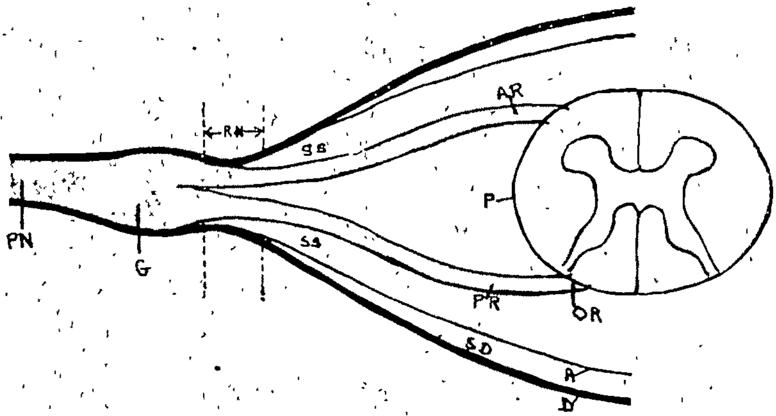


Fig. 1.—Diagram of the radicular nerve and its relations. A, arachnoidal membrane; AR, anterior nerve root; D, dura mater; G, posterior root ganglion, OR, Obersteiner-Redlich area; P, pia mater; PN, peripheral nerve; PR, posterior nerve root; RN, radicular nerve; SS, subarachnoid space; SD, subdural space. (After Richter, from Nageotte's scheme.)

The theory that syphilitic toxins acting through the medium of the cerebrospinal fluid are responsible for the lesions of tabes has received some support, though the part of the nervous system which is primarily affected has been much disputed. Orr and Rows [21] believed that syphilitic toxins could attack the nerve-fibres in any part of their course, but later [22] [23] suggested that the site of elective attack was that part of the posterior roots internal to the Obersteiner-Redlich area where they lose the sheath of Schwann. In their extramedullary course the posterior roots are protected from the effect of toxins by this sheath; on losing this they become vulnerable. Strümpell [39] and Sepp [35] placed the site of action of the toxins inside the spinal cord, but maintained that it is not the toxic cerebrospinal fluid which acts directly on the posterior columns but a toxic exudate from the meninges. The toxic agency of the meningitis was also held responsible for the tabetic lesions by Bresowsky [3], but he placed the lesion at the Obersteiner-Redlich area and not in the spinal cord itself. Alford [1], by the injection of iron salts into the subarachnoid space and subsequent fixation with hydrochloric acid, demonstrated that iron granules were carried into the spinal cord along the posterior roots for some distance, particularly in the lumbar region, and that no granules were carried along the anterior roots. He therefore concluded that syphilitic toxins in the meningeal spaces travel along the posterior roots in the same way, and that the initial lesion consists in a degeneration of the entering root fibres just inside the Obersteiner-Redlich area, where the toxins come into contact with them.

Spielmeyer has been the chief protagonist of recent years of the endogenous, "primary degeneration" theory, but in one paper [37] he has made statements which appear to be contradictory. After quoting his observations that degeneration of the posterior roots takes place almost entirely within the spinal cord, he agrees with Obersteiner and Redlich that the process begins just inside the pia mater where there is a natural constriction of the roots, but he then proceeds to consider the degeneration of the central prolongations of the posterior roots in the posterior columns as a "systemic independent disease process," and says definitely that "there is no evidence that this follows changes at the Obersteiner-Redlich area." It is difficult to reconcile the two statements. In another communication [36] Spielmeyer quotes a case which, in view of the short history and the detailed histological examination, is of importance from the point of view of the earliest lesions, and will therefore be briefly summarized :—

The case was that of a man who died at the age of 56, after having had typical tabetic symptoms and signs for nine months only. Four weeks before death mental symptoms appeared. Histologically, in the spinal cord from the level of the first sacral segment to the first lumbar there was seen typical degeneration of the posterior columns. Above this level the degeneration corresponded to the roots from these regions. With Scharlach R. stain much degenerating myelin was stained in the root entry zone and in the area corresponding to the continuation of these fibres into the posterior columns. In the root regions the first sacral and lowest lumbar segments were the most affected. Degeneration did not extend into the root bundles, but ceased at the place where the roots take on their peripheral character, i.e., at the Obersteiner-Redlich area. Spielmeyer could find no degeneration peripheral to this. Meningeal changes were few, and consisted solely in slight infiltration of the pia-arachnoid, mainly in the cervical region, with small lymphocytes. The only change seen in the nerve roots was a slight infiltration under the dura with lymphocytes, and this only in a few nerve roots. Spielmeyer felt justified in concluding from this case that the essential pathological process in tabes consists in an independent degeneration of the intramedullary posterior roots, which stops short at the place where they take on a peripheral character, i.e., the Obersteiner-Redlich area, the boundary between neuroglial and connective tissue.

Richter [31] attempted to show that the discrepancy between the degeneration in the intra- and extra-medullary roots observed by Spielmeyer was apparent rather than real by conducting experiments on cats. He sectioned the extramedullary posterior roots to determine whether this injury would cause the intra- and extra-medullary roots to degenerate at the same rate. Eighteen days after section of the extramedullary roots myelin degeneration in them had reached the lipoid stage, whilst in the intramedullary roots only the Marchi stage had been reached. Therefore, at the time when lipoid material would stain in the intramedullary roots, it would have disappeared from the extramedullary roots. Richter also pointed out that as one root alone may be affected by the tabetic process for months or even for years, it is possible at an advanced stage in the disease to find in adjacent roots the early phase of the breaking up of myelin and more advanced lipoid changes. The validity of Richter's objection to Spielmeyer's conclusions from this early case rests on the answer to the question how far experimental section of roots can be considered analogous to the slow process which causes degeneration of the roots in tabes.

The theory which found most general acceptance until Richter propounded his "specific granuloma" theory was that of Nageotte [16]. The case on which he founded his localization of the primary lesion was one of dementia paralytica, with very slight posterior column degeneration. Nageotte came to the conclusion that the primary lesion was limited to that part of the posterior root which lies between the point where it leaves the subarachnoid space to join with the anterior root and the spinal ganglion. This part of the posterior root Nageotte called the "radicular nerve." The nature of the lesion he considered to be an interstitial "radiculitis," by which he meant an infiltration with lymphocytes, plasma cells, and what appeared to him to be embryonic cells, with fibrosis of the interstitial tissue of the nerve limited to the area of the posterior root. The degeneration of the posterior root he took to be a secondary phenomenon due to pressure from the infiltrating tissue. Nageotte explained the escape of the anterior roots in this situation by supposing either that they were less susceptible to this particular form of trauma, or that they were capable of regeneration. His own definition [18] of the pathological entity of tabes summarizes very well his view of its pathogenesis: "Tabes is characterized anatomically by an inflammatory lesion which attacks a certain number of sensory or motor roots at their exit from the subarachnoid space and which is dependent upon generalized syphilis of the meninges." He was insistent [19] that meningitis, although invariably present, does not itself cause tabes except through the intermediary of the radiculitis, and that this affection of the radicular nerve is the sole criterion of the tabetic process. Thomas and Hauser [41] confirmed Nageotte's findings of inflammatory changes in the radicular nerve. They also found a constant meningitis in each of their eleven cases, which was sometimes more extensive over the anterior roots than over the posterior. Similar observations were made by Schroeder [34], and by Bresowsky, who found infiltration of the pia-arachnoid in every one of the forty cases he examined.

Jakob [12], Hassin [7] [8], and Schaller [33] have also reported constant inflammatory changes in the meninges. The opinions of two of these writers on the relationship of these findings to the pathogenesis of tabes will be dealt with later in discussing their attitude to the Richter theory.

This theory, formulated by Richter in an exhaustive study, has been accepted up to the present time as the one which best explains the clinical course of the disease. Richter holds the view that the primary and essential lesion in tabes is the settling down of spirochætes from the cerebro-spinal fluid in elective parts of the cerebro-spinal axis. These sites of election are the radicular nerves. The spirochæte then acts as a "formative irritant," and a specific granulation tissue is formed which has its origin in the lymph spaces of that part of the common sheath which lies nearest to the ganglion. This granulation tissue spreads into the perifascicular spaces and the radicular nerve is eventually enclosed by this mass of newly-formed tissue. In late stages of the disease the granulation tissue undergoes regressive changes and becomes sclerosed, thus pressing upon the nerve-fibres and destroying them. Richter's own description [29] of the lesion is: "The granulation growth in the lymph and tissue spaces is the initial, primary and autonomous change in tabes. The extension of the process to the root-nerve causes a secondary root affection."

No lymphatics have hitherto been described in the radicular nerve or in the meninges; neither have spirochætes yet been demonstrated in the cerebro-spinal fluid of tabetics. But apart from these hypothetical considerations the question of the specificity of this "granulation tissue" has to be investigated. Richter described the cells of which it consisted as endothelial in type, but capable in the later stages of the disease of forming fibroblasts. As Hassin [9] has recently pointed out, these cells bear a very strong resemblance to the arachnoidal cells, and they are by no means "specific" for tabetic nerve-roots. Hassin observed them around the periphery of several normal nerve-roots, and it is hoped to show in this study that they are constantly present in considerable numbers in nerve-roots throughout the spinal axis and that they may even be perifascicular.

Richter [30] strenuously denies the presence of any inflammatory changes in the radicular nerve in cases of pure tabes. These occur, he says, only in cases of tabo-paresis and are then due entirely to the paretic factor. Hassin agrees with Richter that hæmatogenous elements play no part in the lesion of the radicular nerve. Jakob, on the other hand, found plasma cells and lymphocytes infiltrating the radicular nerve in cases of pure tabes, though he is inclined to the opinion that these may be histogenous rather than hæmatogenous. The question of a difference in intensity between the affection of the roots in their intra- and extra-medullary course, that is, at their point of entry through the pia mater at the Obersteiner-Redlich area, is summarily dismissed by Richter as he does not believe that this difference has been proved.

Meningitis is, according to Richter, a common syphilitic accompaniment of tabes but not a constant change, and it consists in an inflammatory lesion of the pia-arachnoid entirely independent of the tabetic process, and also independent of the posterior column degeneration. The frequency with which meningitis occurs in tabes depends on both lesions being caused by the presence of the spirochætes in the subarachnoid space, but in tabes the spirochæte settles in the root-nerve and in meningitis in the pia mater. The difference in reaction is due to the anatomical peculiarities of the two sites.

The posterior column degeneration is considered by Richter to be secondary to the lesion in the radicular nerve. In his twenty-four cases he could find "no indication which would allow him to accept any independent degeneration in the spinal cord."

He stresses, as additional evidence to his experimental work, the not uncommon cases in which the posterior column degeneration is asymmetrical, and remarks that in most cases a true asymmetry unrevealed by coarse staining methods really exists between the degeneration on the two sides which is probably due to variability in the numbers of spirochætes settling in the corresponding roots and therefore to differences in the intensity of the granulation process.

Changes in the posterior root ganglia Richter also considers secondary to the lesion of the radicular nerve as they are analogous to those found by Köster [13]. after experimental section of the posterior roots. Excess of lipochrome pigment, shrinkage of the ganglion cells and hyperplasia of the capsular nuclei were the changes most often observed. Chromatolysis occurred only very rarely. The resistance of individual ganglion cells plays a large part in determining the extent of the lesion, as some ganglia from a certain case may be severely damaged whilst others appear normal. No inflammatory changes were seen in cases of pure tabes, but in the cases of tabo-paresis both perivascular and diffuse infiltrations with lymphocytes and plasma cells were found extending into the ganglia from the corresponding root-nerves.

Richter [29] also investigated the changes in the cranial nerves. It is not proposed to deal here with his findings in any detail, but briefly, he described amongst the extracerebral fibres of the third and fifth nerves a granulation tissue identical with that which he observed in the radicular nerves. In the optic nerves of cases with optic atrophy no granulation tissue was seen, but there was a vascular reaction characterized by infiltration with plasma cells and lymphocytes. This difference in reaction Richter explains by the fact that the optic nerve is developmentally of central origin and therefore reacts to noxious stimuli in the same manner as the central nervous system.

But the support that was given to Richter's theory was due not to his description of a "specific" tissue, but to the fact that he had been able to demonstrate spirochætes in this tissue in three cases out of nine of pure tabes and in one case out of four of tabes with spinal syphilis.

Most of the criticism that has been directed against Richter's theory has come from Jakob [11], from Wohlwill [45], and from Spielmeyer [36]. The latter could not convince himself that Richter's findings were at all constant. His views have already been given.

Jacob emphasizes the constant spinal meningitis observed by him and also by Hassin in the material studied by him in Jakob's laboratory. He points out that whilst Hassin regards the changes in Nageotte's area as the most important, Richter looks upon the specific lesion in this region as the only one of importance.

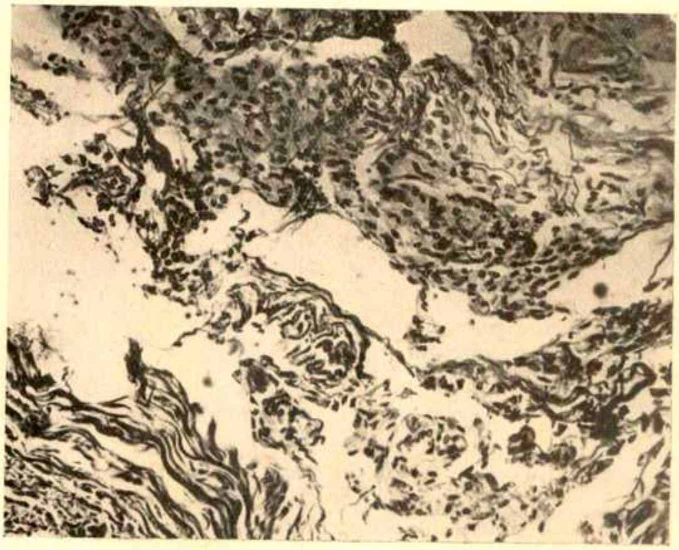


FIG. 2.—Section through the radicular nerve of a case of uncomplicated tabes, stained with hæmatoxylin and counterstained with van Gieson. Two arachnoidal tufts are present and extend between the nerve-fibres.

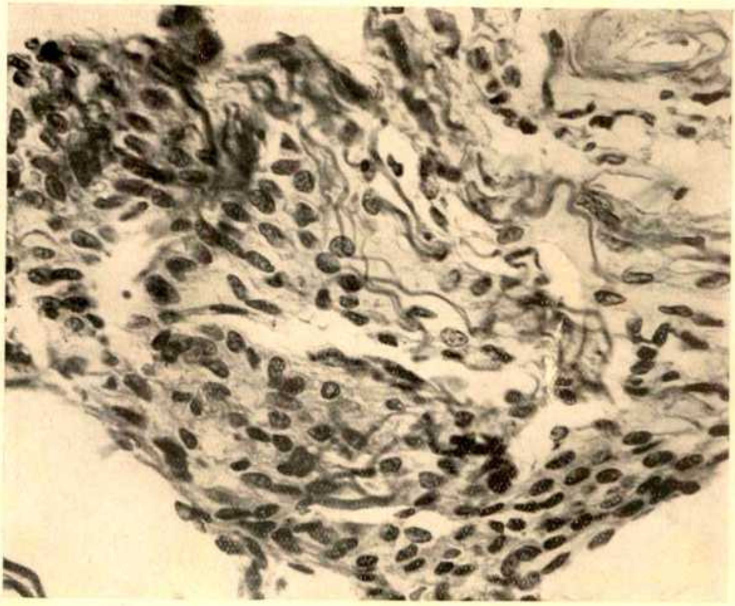


FIG. 3.—A portion of the same section as fig. 1, under higher magnification to show the endothelial character of the infiltrating arachnoidal cells.

To illustrate paper by R. O. Stern.

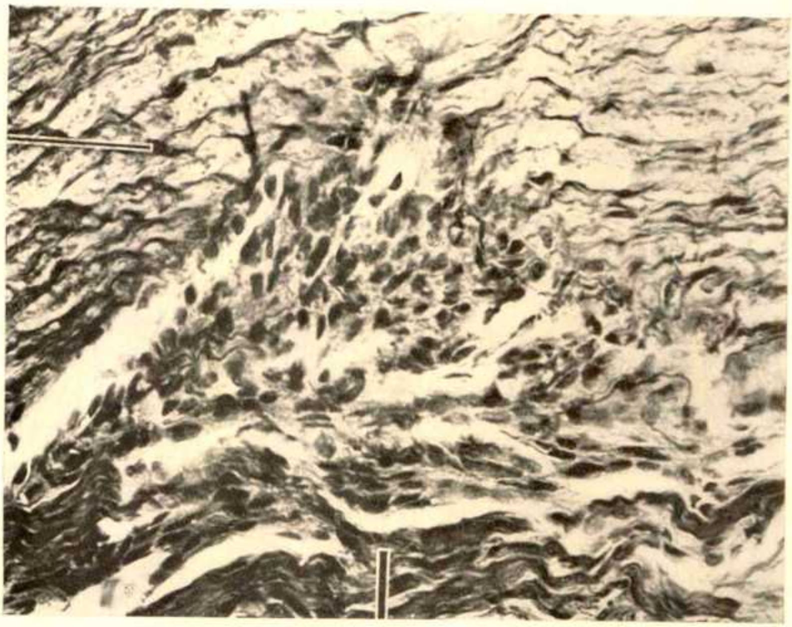


FIG. 4.—Section through the radicular nerve of a case of subacute combined degeneration of the cord stained with hæmatoxylin and counterstained with van Gieson. An arachnoidal tuft can be seen infiltrating the nerve-fibres. Isolated arachnoidal cells are also present and lie between nerve-fibres.

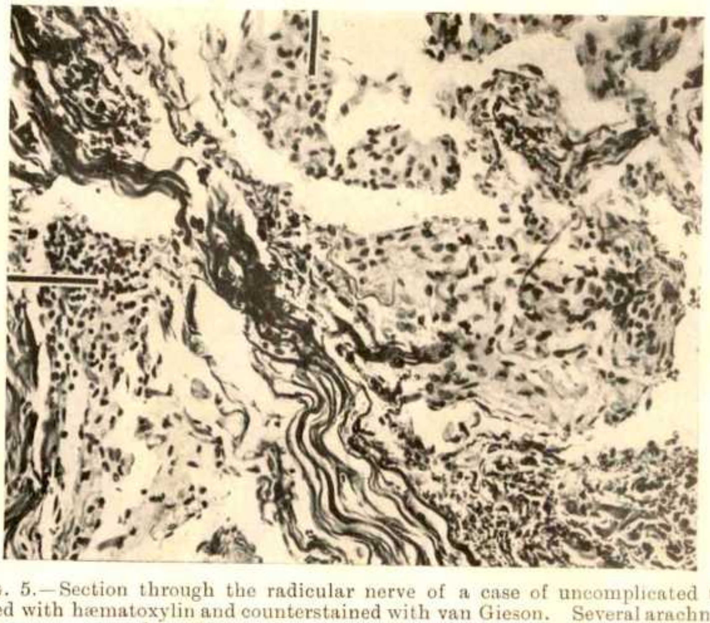


FIG. 5.—Section through the radicular nerve of a case of uncomplicated tabes stained with hæmatoxylin and counterstained with van Gieson. Several arachnoidal tufts are present, and in addition there is much infiltration with small lymphocytes.

To illustrate paper by R. O. Stern.

Jakob is of the opinion that although the granulation tissue described by Richter undoubtedly occurs in Nageotte's area, its distribution is not limited to this area but extends to the arachnoid covering the spinal cord. He found infiltrations with lymphocytes and plasma cells as well as granulation tissue in the Obersteiner-Redlich area in cases of pure tabes, and is convinced that damage to the nerve-fibres in this region is an important contributory factor in causing degeneration of the intramedullary posterior roots.

Wohlwill criticizes Richter for his interpretation of his histological findings as a new growth of granulation tissue which actually destroys the nerve-fibres by invasion and ultimate strangulation. The process as conceived by Richter resembles, according to Wohlwill, that seen in infiltration by a malignant neoplasm rather than pressure from sclerosing granulation tissue. Richter does not mention other possible ways in which this tissue could injure the nerve-fibres, as, for example, by the blocking up of lymph channels or other nutritional disturbances. Wohlwill also draws attention to the fact that the case which Richter describes as one of "incipient tabes" had had symptoms for three years, and can therefore not be accurately described as representing the earliest stages of the disease process.

Hassin has recently published a paper in which he presents a modification of Richter's hypothesis on the effect of the granulation tissue in the radicular nerve on the tabetic process. Hassin does not consider that the cells composing the "granulation tissue" in Nageotte's area are specific formations caused by the presence of the spirochæte in the cerebrospinal fluid, but that they are arachnoidal cells which have proliferated in response to irritation from an inflamed dura mater, which is a lesion constant in tabes. These cellular masses obstruct the perineural spaces by invading them and interfere with the escape of cerebrospinal fluid from the subarachnoid space. Stasis of the cerebrospinal fluid therefore occurs, and as, according to Hassin, drainage of the tissue fluids from the posterior columns is performed chiefly through the perineural spaces of the posterior roots, this part of the spinal cord is the first to undergo degeneration. Hassin cannot accept the mechanical "strangulation" theory of Richter, as the invading arachnoidal cells are rarely found between the fasciculi in the radicular nerve; they are usually confined to the margins of the fasciculi. Moreover, they are practically never seen in relation to the nerve-fibres.

But Hassin, after having advanced his modification of Richter's theory and having described the degeneration of the posterior columns of the spinal cord as a secondary phenomenon due to a "tissue fluid stasis" caused by blocking of the perineural spaces, goes on to state that the degeneration of the posterior columns must be considered a primary process which originates within the spinal cord itself. This degeneration was seen in the form of an "island-like" degeneration, which Hassin considers typical of tabes, the islands consisting of demyelinated areas in which the nervous elements are mainly replaced by neuroglial tissue, although thin axons are usually preserved.

But if Hassin's theory is correct and the degeneration of the posterior columns is caused by retention of tissue fluids we should expect to find the amount of degeneration in the posterior columns to correspond more or less exactly to the intensity of the arachnoidal infiltrations.

Other lesions observed by Hassin agree with those already described by many other writers. But in the spinal ganglia he found evidence of satellitosis and neuronophagia in addition to shrinkage of cells and excessive accumulation of pigment in the ganglion cells.

SPIROCHÆTES IN TABETIC LESIONS.

The only positive spirochæte findings recorded in tabes previous to Richter's were those of Noguchi [20], who found one or two spirochætes in the posterior columns of a case of tabes complicated by meningo-myelitis, and of Versé [42], who claimed to have found them in two cases: in one in the spinal ganglia, lying in the ganglion cells and also between them, in the other in the nerve roots. Richter rather doubted Versé's results on the ground that impregnated nerve-fibres closely resemble spirochætes. Richter used Noguchi's method and mentions that Jahnel's method was unsuccessful even in those cases which were positive by Noguchi's method. This is surprising as Jahnel's method has been found to give consistently good results in this country. Richter found only very few spirochætes in his positive cases, and of these, relatively morphologically intact forms were very rare. Most of them were degenerated forms and little heaps of "degenerated spirochæte fragments" were seen. The spirochætes were found only in the "granulation tissue" with one solitary exception, which was found in the thickened covering of a root bundle. Richter contends from many negative findings that there are tabetic root nerves in which no spirochætes occur.

There is no reason for supposing that spirochætes were not present in the tissue which Richter described, especially as one of his sections was confirmed by Jahnel, but it is possible if the "granulation tissue" is composed of arachnoidal cells that spirochætes have been "swept in" to the perifascicular spaces together with these cells, and that they are to be considered as a fortuitous finding. Jahnel [10] found spirochætes in the subarachnoid spaces of one case which he examined with the dura mater intact. It is possible that in this case the spirochætes were really present in the subdural space, and that this is their usual habitat in tabes. This would explain the negative findings of many observers, as the dura is but rarely included in sections of the spinal cord.

It is here convenient to summarize those theories of the pathogenesis of tabes which have been considered:—

(1) A primary degeneration of the intramedullary posterior roots. (Charcot and Pierret, Westphal, Strümpell, Flechsig, Sepp, Spielmeyer.)

(2) Meningeal inflammation causing direct pressure on the posterior roots at their passage through the pia mater. (Obersteiner and Redlich.)

(3) Influence of syphilitic toxins on the posterior roots. (Orr and Rows, Marie and Guillain [15], Bresowsky, Alford.)

(4) Inflammatory changes in the radicular nerve. (Nageotte, Thomas and Hauser.)

(5) Granulomatous formation in the radicular nerve. (Richter.)

(6) Retention of tissue fluids in the spinal cord, due to obstruction by proliferating arachnoidal cells. (Hassin.)

Certain writers, notably Jakob and Schaffer [40] (in his article in Lewandowsky's "Handbuch der Neurologie"), do not consider that any one theory will explain all the clinical phenomena, and they therefore regard the pathological process in tabes as consisting of a combination of two or more of the processes enumerated above. The conclusions arrived at from the results of this study will be given later.

REPORT ON PATHOLOGICAL MATERIAL INVESTIGATED.

The material at my disposal was derived from nine cases of pure tabes, three cases of tabo-paresis and eight cases of general paralysis. In addition, the posterior root ganglia from twenty-seven cases taken at random from the post-mortem material available, which included examples of most of the common diseases of the spinal nervous system and three cases in which the spinal cord and its meninges could definitely be said to be normal, were examined as controls. The Gasserian ganglia complete with dural sheaths from two normal cases were also examined.

The duration of symptoms in the tabetic cases varied from twenty months to twenty-one years. In two cases of pure tabes no clinical history was available, but the cases were obviously of long standing from the amount of sclerosis present in the ganglia and roots. In two cases of taboparesis the cerebral and spinal symptoms appear to have developed at the same time, the total duration of symptoms being twelve months in one case and six months in the other. In the third case the history was that of a "nervous breakdown" eighteen months previously, but only three months prior to admission had there been symptoms of a spinal lesion. This case already exhibited the typical tabetic signs of Argyll Robertson pupils, partial analgesia to pinprick over the chest, ataxia and inco-ordination of both legs with absent knee and ankle jerks, and it seemed probable, in view of the very short history, that here was a case which should show the earliest tabetic lesions.

Sections of the posterior root ganglia were made longitudinally to include the radicular nerve and posterior-root and, wherever possible, ganglia from the cervical, dorsal and lumbar regions were examined. Similar regions of the spinal cords were sectioned, with their meninges and roots attached.

MICROSCOPICAL EXAMINATION.

The staining methods employed were those of hæmatoxylin with van Gieson's counterstain for the ganglia and posterior roots, Scharlach R., hæmatoxylin with van Gieson, Kultschitsky-Pal and (in the more recent cases) Bielschowsky, for the spinal cord.

Sections from all the syphilitic posterior root ganglia and from the spinal cords of the pure tabes cases were stained by Jahnel's method for spirochætes.

As the main purpose of this study was to investigate the changes in the radicular nerve from the point of view of the Richter hypothesis, the lesions detected in them will be considered first. Except where differences existed between the lesions in the cases of pure tabes, tabo-paresis and general paralysis, the descriptions given below cover the three types of case.

(1) *Infiltrative lesions.*—Epidural infiltration with lymphocytes and plasma cells was common, but was present to the greatest extent in the cases of general paralysis and tabo-paresis. It may be stated here that in the cases of general paralysis and tabo-paresis plasma cells were more commonly observed in hæmatogenous infiltrations than they were in cases of pure tabes. The infiltrating cells were frequently found in small clusters or heaps, as well as lying scattered throughout the epidural space.

Subdural infiltrations with lymphocytes and plasma cells, although less generally seen in the cases of pure tabes, certainly occurred in the majority of cases, particularly in relation to the blood-vessels. In the cases of general paralysis and tabo-paresis these infiltrations were constant and, in a few cases, particularly those of tabo-paresis, the focal arrangement of the infiltrating cells was striking. The cells did not in most cases penetrate between the nerve-fibres, but occasionally some could be seen separating the nerve elements. More often the cells were limited to the periphery of the nerve-bundles.

(2) *Vascular changes.*—The walls of the blood-vessels in the radicular nerve were much thickened in cases of pure tabes of any standing, and in all cases there appeared to be at first sight a great excess of that peculiar degeneration of blood-vessels which gives rise to "corpora arenacea" or psammoma bodies. But on comparing the numbers of these bodies in normal radicular nerves with those in the tabetic nerves it was found that normal nerves contained as many, if not more, of these bodies than did the tabetic ones.

It is necessary to point out that the age of the arteries plays no part in the development of these bodies, as they were found in considerable numbers in the nerves of a boy aged 19. The mode of production of these bodies from blood-vessels is quite unknown. They are mentioned here only to demonstrate that their presence in large numbers in the radicular nerves in tabes has no connection whatsoever with the tabetic process.

(3) *Fibrosis of meninges.*—The dura mater covering the radicular nerves and ganglia was thickened in every case examined, but the thickening was greatest in the most long standing cases of pure tabes. The perineural sheaths of the radicular nerves were slightly thickened in all cases of pure tabes, but a true fibrosis affecting the nervous elements by pressure was seen only in one case, that of twenty years' duration.

(4) *Richter's specific "granulation tissue."*—In considering the "granulation tissue" which Richter described, it must be noted that Hassin has already recognized the cells of which this tissue is composed in the radicular nerves of non-syphilitic cases. Some years before the appearance of Hassin's paper Dr. Greenfield and Dr. Wolfsohn observed these cells during their investigation, in this laboratory, of the radicular nerves in a case of the Charcot-Marie-Tooth type of muscular atrophy, but they did not publish their observation. They have kindly given me the opportunity of examining sections of the radicular nerves from this

case, and in addition sections have been taken from the following cases (the age of the patient is given in parenthesis after the disease).

Four cases of disseminated sclerosis (51, 46, 43, 30).

Four cases of subacute combined degeneration of the cord (63, 60, 54, 49).

Three cases of secondary carcinoma involving the spine (60, 53, 40).

Two cases of disseminated myelitis (37, 32).

Two cases of sarcoma of the spine (63, 29).

Five cases of syphilitic myelitis (53, 46, 44, 30, 27).

One case each of peripheral neuritis (48), tuberculosis of the spine (51), chloroma (19), cerebral hæmorrhage (74), cerebral thrombosis (69), cerebral abscess (50), and fracture of the spine (50). Also, the Gasserian ganglia were examined from two cases; one a case of cerebello-pontine angle tumour (25), the other a cerebral abscess (29).

My observations agree with those of Greenfield, Wolfsohn and Hassin. There is no evidence that the cells of which this "granulation tissue" is composed are newly formed, and it is quite clear that their existence does not necessarily depend on the presence of the spirochæte since they were present in twenty-two out of the twenty-seven control cases. They differ in no wise in histological appearance from the simple arachnoidal cells of the arachnoid membrane. These are characterized by having oval nuclei with a very distinct nuclear membrane, inside which the chromatin is arranged in a stippled or dotted manner; they are in fact characteristic endothelial cells. The suggestion of Richter that these cells can and do become transformed into fibroblasts in the late stages of tabes is not confirmed by my observations. The appearance of the cells in a case of three months' duration (tabo-paresis), or in a case of pure tabes of twenty months' duration, is identical with that in cases of pure tabes of five, ten, or even twenty years' duration. If it were possible that these cells could undergo metamorphosis, some intermediate stage between an endothelial type of cell and a fibroblastic type would be seen in material from cases which varied so much in duration.

Hassin rightly contended that these cells very rarely penetrate between nerve-fibres; they are almost invariably confined to the periphery of the nerve bundles. He believes, however, that not only is the actual number of arachnoidal cells in the radicular nerve increased in tabes, but that in this condition they occur in the radicular nerves at all levels of the spinal cord, whilst in normal cases the cells are seen only at one level—at which level and why is not stated.

In this study radicular nerves from the cervical, dorsal and lumbar regions of twenty-seven control cases were examined and arachnoidal cells were found at all these levels, although they were not found at every level in every case. Furthermore, they may infiltrate the nerve-bundles in non-tabetic cases, and even appear between the nerve-fibres. Such an appearance is illustrated in fig. 3 from a case of subacute combined degeneration of the spinal cord. Their numbers in non-syphilitic cases may equal and even exceed those in tabetic cases. Only those cases of tabes with much generalized arachnoiditis showed an excessive number of arachnoidal cells in the radicular nerve. It is probable that in these cases the prolongations of arachnoidal membrane into the radicular nerve share in the general proliferation of arachnoidal cells.

It is clear therefore, in the first place, as Hassin has already pointed out, that the cells of Richter's "granulation tissue" are not specific for tabes, and in the second place, as they may occur in normal radicular nerves in like number and with the same distribution as in tabes, they can have no essential connection with the pathological process of this disease.

Reference has already been made to the integrity of the nervous elements in the radicular nerve except in cases of long standing. This is in accordance with the findings of Hassin. Although Richter described destruction by pressure of the nerve-fibres in this region it must be remembered that the duration of symptoms in his least advanced case was three years.

CHANGES IN THE SPINAL GANGLIA.

In several cases of general paralysis and of tabo-paresis there were definite inflammatory changes in the spinal ganglia with infiltration with lymphocytes and plasma cells, but in only one case of pure tabes were there inflammatory changes. There was much fibrosis of the spinal ganglia in three long-standing cases of pure tabes. The most noteworthy lesions found in all the ganglia were hypertrophy of the capsule cells of the ganglia and an increase in the pigment content of the ganglion cells. In many cases the ganglion cells appeared to be shrunken, but as much of the material had been preserved for some years, and the majority of the preparations of the ganglia had been embedded in paraffin, it is difficult to decide how much of this shrinkage was due to artefact and how much to cellular change. As Orr and Rows pointed out many years ago, most of the changes described in ganglion cells are the result of artefact or bad fixation. Certainly no confirmatory evidence of degeneration of these cells, as chromatolysis or neuronophagia, could be detected in my series.

THE SPINAL MENINGES.

The spinal meninges were thickened in all cases of pure tabes, the pia being especially affected. The thickening was not more evident in the area of the entry of the posterior root than in that of the anterior root. There was no variability in the degree of thickening in the several regions of the spinal cord. In one case changes in the meninges had to be disregarded in relation to the tabetic process, as a septic meningitis had occurred following operation for relief of tabetic crises. Of the other eight cases four exhibited considerable cellular infiltration of the pia with small lymphocytes and a few plasma cells, whilst in the other four cases lymphocytic infiltration was very slight, though not completely absent. In no case could it be observed that the infiltration of the pia was confined to, or greater in, the region of the posterior roots. In long-standing cases the vessels of the pia were thickened and perivascular infiltration with lymphocytes was not uncommonly found. In the cases of paralysis and tabo-paresis inflammatory phenomena in the meninges were much more intense, although thickening of the meninges was not so great as in the pure tabes cases. Plasma cells were very numerous and perivascular infiltration with lymphocytes was not uncommonly found. No difference in degree of infiltration between the posterior and anterior root regions could be determined.

THE SPINAL CORD.

In describing the lesions in the spinal cord it is convenient to take the three types of case separately. Kultschitsky-Pal preparations of the spinal cord in the pure tabes cases revealed the characteristic picture of posterior column demyelination with the incidence greatest on those nerve-fibres which represent the lumbar roots, and which in the lumbar region are confined to the postero-external part of the posterior columns, in the "bandelette of Pierret." Why these fibres should be the first to degenerate is unknown. Richter's theory that the lumbar roots are first affected because they run vertically and the spirochætes sink by the force of gravity into their meningeal coverings and there cause the specific reaction, cannot be entertained seriously.

The rate of degeneration of the fibres varies within wide limits.

It was surprising to find that in a case with a history of five and a half years' duration which was characterized by the occurrence of violent gastric crises with very few symptoms of ataxia or inco-ordination, but with typical signs (e.g., Argyll-Robertson pupils, breast plate analgesia, absent ankle-jerks), practically no posterior column degeneration could be made out in any region of the spinal cord. The only lesion appeared to be the loss of a few myelinated fibres in the root entry zone of the mid-dorsal region. In this case there were considerable inflammatory changes in the radicular nerves.

By way of contrast, in the case of pure tabes with the shortest history—of twenty months only—most extensive posterior column degeneration was present.

The cases of tabo-paresis were most instructive from the point of view of posterior root degeneration. In the case with a history of spinal symptoms of only three months' duration, very little demyelination was expected in the posterior columns. Advanced myelin degeneration was found, however, in the lumbo-sacral region and could be traced upwards in the cord to a corresponding degeneration of most of the column of Goll in the cervical region. The degeneration had already reached the lipoid stage and was well seen in Scharlach R. preparations. Droplets of fat could be traced outwards to the most external part of the root entry zone, but they did not extend into the extramedullary portion of the roots, in which the myelin was normal.

In this case most of the degenerative products of myelin were in the same stage, therefore degeneration of the posterior roots must in some cases at any rate occur very rapidly, as it did in this case. Degeneration of these roots is therefore not always due to a slow strangulation such as Richter suggests.

In another case of tabo-paresis with a history of six months' duration, no posterior column degeneration could be determined. It was impossible to determine which factor differed in the two cases. Meningeal infiltration, inflammatory changes in the radicular nerves, arachnoidal proliferation, did not seem to vary to any extent in the two cases.

In the third case of tabo-paresis, although no lipoid substances could be stained by the Scharlach R. method, Kultschitsky-Pal preparations showed that myelin degeneration was present in the posterior columns of the lumbar region. At the end of twelve months therefore a stage had been reached in which lipoid substances had already been removed—further evidence of the rapidity with which degeneration can in some cases take place in the intramedullary roots. The cases of uncomplicated general paralysis were also examined by fat-staining methods to determine whether any posterior root degeneration was present. None could be detected. Jakob's opinion that it is permissible to include cases of tabo-paresis with spinal symptoms amongst cases for the investigation of early tabetic lesions is therefore confirmed. Lesions which occur in parts of the nervous system which are not affected by pure general paralysis should not be ascribed to the paretic process.

RESULT OF EXAMINATION FOR SPIROCHÆTES.

The examination of the radicular nerves, spinal ganglia and spinal cords for spirochætes must be reported negative, for although in one case of pure tabes a single spirochæte-like body was seen in the posterior column of the cord, it was not typical and no others could be found in other sections from the same case. It is not justifiable therefore to regard this as a positive finding. Many structures which stained deeply with silver were encountered in the ganglia and radicular nerves. These might have been degenerating spirochætes or products of their degeneration. They were certainly neither nerve-fibres nor deposits of silver, but because not one typical form could be seen these structures were rejected as positive results.

DISCUSSION.

The results of this study have in the main been more destructive than constructive. Evidence has been brought forward that the theory of pathogenesis propounded by Richter does not bear the test of investigation. In the first place the cells of which his "specific granulation tissue" is composed are not specific for tabes, as Hassin first pointed out (although he was not the first to make the observation); they are arachnoidal cells and they may occur with the same distribution and in equal numbers in the radicular nerves of normal cases. These cells were seen in this situation in twenty-two out of twenty-seven control cases, and in two controls they were found around the periphery of the nerve-bundles of the fifth nerve as it enters the Gasserian ganglion. Secondly, the degeneration which occurs in the intramedullary part of the posterior root may be present as early as three months after the onset of symptoms, whilst eighteen months after the onset of symptoms suitable staining methods may demonstrate the presence of a lesion of the myelin sheaths in the posterior columns of long standing. On account of the rapidity of the degeneration in the intramedullary roots in certain cases, therefore, Richter's theory of a slow strangulation of the posterior roots by this "granulation tissue" is untenable.

The theory of Hassin is subject to criticism from several points of view. But the whole theory is founded on a fallacy because in normal cases with similar arachnoidal infiltrations there is no degeneration of the posterior columns. Further, in tabetic cases there is no correspondence between the intensity of the arachnoidal infiltrations in the radicular nerves and the amount of posterior column degeneration.

The whole problem of the site and nature of the primary lesion in tabes turns upon the point that we do not know for certain where it is the spirochæte first settles in the nervous tissues. In spite of many attempts to find the spirochæte in tabetic lesions, only four observers have been successful. Noguchi found a few in the posterior columns of one case. Versé described them in the spinal ganglia and posterior roots of two cases. Jahnel [10] discovered a very few in the meninges of one case when he examined the spinal cord with the dura mater intact. Richter has described them (and one of his sections was confirmed by Jahnel) in the arachnoidal proliferations. They have never been described as occurring in the subdural space, though they may possibly exist in this situation as Jahnel was only able to find them in a case in which the dura was intact.

But it may not be necessary for spirochætes to be present constantly in the central nervous system in order to produce tabetic lesions. Orr and Rows [24] [25] showed clearly that bacterial toxins will pass along the afferent nerves by the perineural lymph-stream without causing any changes in the peripheral nerves and will produce degeneration of the posterior columns of the spinal cord indistinguishable from that of tabes. They introduced capsules containing different bacteria in contact with the afferent nerves of animals and produced posterior column degeneration. They also observed a similar degeneration in the spinal cords of patients who died following peripheral septic lesions, e.g., boils, superficial abscesses. If we accept the possibility that a tabetic degeneration may also be caused by the toxins from spirochætes which exist outside the central nervous system, then it is necessary to find a focus in which the spirochætes may live for many years whilst pouring out their toxins along the afferent nerves. It is well known that certain parts of the body offer a suitable nidus for harbouring spirochætes for many years. The aorta is the chief of these. MacIntosh and Fildes [14] did not correlate aortitis with tabes, but they pointed out that in many cases examined at random post mortem a syphilitic aortitis was the only demonstrable syphilitic lesion, and that the aorta was a possible source of spirochætes which might wander out into other tissues of the body.

at intervals and cause various syphilitic manifestations. Spirochætes have not been found in the aorta in tabes, but Jahnel has found them there in general paralysis. In my study attempts were made to find them in the aortas available in two cases of tabo-paresis (in one of which spirochætes were present in the cerebral cortex), in one case of pure tabes, and in one of general paralysis, but without success. Further work on this aspect of the subject is necessary.

SUMMARY AND CONCLUSIONS.

(1) A review of the most important theories of the pathogenesis of tabes has been given.

(2) A series of cases of uncomplicated tabes, of tabo-paresis and of general paralysis has been studied with special reference to the lesions in the radicular nerves and the Richter theory of pathogenesis. In addition a series of twenty-seven control cases has been studied for comparison.

(2) Evidence has been brought forward to prove that neither Richter's theory nor Hassin's modifications of it is capable of explaining the pathogenesis of tabes.

(4) Reference is made to the work of Orr and Rows on degeneration of the posterior columns caused by bacterial toxins from peripheral foci and the bearing this work has on the pathogenesis of tabes. The suggestion is made that in tabes the aorta may act as a focus from which spirochætes may exert their toxic effects on the central nervous system.

I wish to thank the Medical Research Council for the grant which has made it possible for me to carry out this work. It gives me great pleasure to acknowledge my debt to Dr. J. Godwin Greenfield for the unfailing assistance and advice he has given me in the preparation of this paper.

BIBLIOGRAPHY.

[1] ALFORD. L. B. "Studies on the Pathogenesis of Tabes dorsalis," *Trans. Amer. Neur. Assoc.*, 1922, **48**, 256.

[2] BOURDON and LUYS. *Arch. gen. de Med.*, November 9, 1861.

[3] BRESOWSKY, M. "Ueber die Veränderungen der Meningen bei Tabes und ihre pathogenetische Bedeutung," *Arb. a. d. Neurol. Inst. Wien.*, 1912, **20**, 1.

[4] CHARCOT, J. M., and PIERRET, M. *Soc. de Biol.*, 1871.

[5] DEJERINE, J. "Maladies de la moelle épinière," Paris, 1909.

[6] FLECHSIG, P. "Ist die Tabes dorsalis eine Systemerkrankung?" *Neurol. Centralbl.*, 1890, **9**, 33 and 72.

[7] Hassin, G. B. "Beiträge zur Histopathologie der Tabes dorsalis," *ibid.*, 1914, **33**, 1138.

[8] *Idem.* "Histopathological Studies in Tabes dorsalis," *Journ. Nerv. and Ment. Dis.*, 1915, **42**, 699.

[9] *Idem.* "Tabes dorsalis, Pathology and Pathogenesis," *Arch. of Neurol. and Psychiatr.*, 1929, **21**, 311.

[10] Jahnel, F. "Die Spirochaeten im Zentralnervensystem bei der Paralyse," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1921, **73**, 310.

[11] Jakob, A. "Einige Bemerkungen zur Histopathologie der Paralyse und Tabes, mit besonderer Berücksichtigung der Spirochätenbefunde," *Arch. f. Psych.*, 1922, **65**, 191.

[12] *Idem.* "Die Entzündungsfrage im Zentralnervensystem," *Jahresk. f. ärzt. Fortbild.*, 1919, **5**, 3.

[13] Köster. "Zur Physiologie der Spinalganglienzellen usw., sowie zur Pathogenese der Tabes," Leipzig, 1904.

[14] MacIntosh, J., and Fildes, P. "Comparison of the Lesions of Syphilis and Parasyphilis," *Brain*, 1914, **36**, 141.

[15] Marie, P., and Guillain, G. "Les lésions du système lymphatique postérieur de la moelle sont l'origine du processus anatomo-pathologique du tabes," *Rev. Neurol.*, 1903, **2**, 43, 103, 108.

[16] Nageotte, J. "La lésion primitive du tabes," *Bull. Soc. anat. de Paris*, 1894, **69**, 808.

[17] *Idem.* "La lésion primitive du tabes," *Compt. rend. Soc. de Biol.*, 1900, **52**, 354, and 1902, **54**, 1226.

[18] *Idem.* "Pathogénie du tabes," *Presse méd.*, 1902, **10**, 1179.

[19] *Idem.* "Pathogénie du tabes," *ibid.*, 1903, **11**, 5.

[20] Noguchi, H. "Studien über den Nachweis der Spirochaete pallida im Zentralnervensystem bei der progressiven Paralyse und bei Tabes dorsalis," *Münch. med. Wochenschr.*, 1913, 737.

[21] Orr, D., and Rows, R. G. "The Nerve Cells of the Human Posterior Root Ganglia and their Changes in General Paralysis of the Insane," *Brain*, 1901, **24**, 286.

[22] *Idem, idem.* "A Contribution to our Knowledge of the Course of the Lymph Stream in the Spinal Roots and Cord," *Rev. of Neurol. and Psychiatr.*, 1903, **1**, 639.

[23] *Idem, idem.* "Lesions of the Spinal Cord as the Result of Absorption from Septic Foci," *ibid.*, 1906, **4**, 25.

[24] *Idem, idem.* "A Clinical and Experimental Investigation into the Lymphogenous Origin of Toxic Infections of the Central Nervous System," *ibid.*, 1907, **5**, 345.

[25] *Idem, idem.* "The Histological Evidence that Toxins reach the Spinal Cord via the Spinal Roots," *ibid.*, 1910, **8**, 721.

[26] Obersteiner, H., and Redlich, E. "Ueber das Wesen und Pathogenese der tabischen Hinterstangsdegeneration," *Obersteiner's Arb.*, 1894, **2**, 158.

[27] *Idem, idem.* "Bemerkungen zur tabischen Hinterstangserkrankung," *ibid.*, 1895, **3**, 192.

[28] Pierret, M. "Note sur la sclérose des cordons postérieurs dans l'ataxie locomotrice progressive," *Arch. de Physiol.*, 1871, **4**, 364.

[29] Richter, H. "Zur Histogenese der Tabes," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1921, **67**, 1.

[30] *Idem.* "Bemerkungen zur Histogenese der Tabes," *Arch. f. Psychiatr.*, 1922, **67**, 295

[31] *Idem.* "Weitere Beitrag zur Pathogenese der Tabes," *ibid.*, 1923-4, **70**, 529.

[32] *Idem.* "Einige Bemerkungen zur Pathogenese der Tabes," *ibid.*, 1924, **72**, 318.

[33] Schaller, W. F. "Pathology of Tabes dorsalis," *Arch. of Neurol. and Psychiatr.*, 1919, **1**, 749.

[34] Schroeder, P. "Ein Beitrag zur Histopathologie der Tabes dorsalis," *Centralbl. f. Nervenheilk. u. Psychiatr.*, 1906, **29**, 585.

[35] Sepp, E. "Ueber die Pathogenese der Tabes," *Deutsch. Zeitschr. f. Nervenheilk.*, 1914, **52**, 46.

[36] Spielmeyer, W. "Zur Pathogenese der Tabes," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1923, **84**, 257.

[37] *Idem.* "Pathogenese der Tabes," *ibid.*, 1924, **91**, 627.

[38] STRÜMPELL, A. "Die pathologische Anatomie der Tabes," *Arch. f. Psychiatr.*, 1882, **12**, 723.

[39] *Idem.* "Pathologie und Behandlung der Tabes dorsalis," *Wien. med. Wochenschr.*, 1911, **61**, 1214.

[40] SCHAFFER, K. "Tabes dorsalis" in Lewandowsky's "Handbuch der Neurologie," 1911, 1022.

[41] THOMAS, A., and HAUSER, G. "Étude sur les lésions radiculaires et ganglionaires du tabes," *Nouv. Icon. de la Salpêtr.*, 1902, **15**, 290 and 412.

[42] VERSÉ, M. "Ueber die *Spirochæte pallida* bei fruh- und spatsyphilitischen Erkrankungen der Nervensystems," *Münch med. Wochenschr.*, 1913, 2446.

[43] VULPIAN, A. "Maladies du Système nerveux," 1879, 257.

[44] WESTPHAL, C. "Ueber das Verschwunden und die Localisation des Kniephanomens," *Berl. klin. Wochenschr.*, 1881, **18**, 1820.

[45] WOHLWILL, F. Criticism of RICHTER'S paper in *Zentralbl. f. d ges. Neurol. u. Psychiatr.*, 1921, **26**, 120.

DIPLOPIA WITHOUT EXTRA-OCULAR PALSIES, CAUSED BY HETERONYMOUS DEFECTS IN THE VISUAL FIELDS ASSOCIATED WITH DEFECTIVE MACULAR VISION.

BY L. S. KUBIE, M.D.,[1]

AND

J. W. BECKMANN, M.D.

(From the National Hospital, Queen Square, London.)

DURING the course of a recent study of tumours of the hypophysis, of the hypophyseal stalk, and of the suprasellar meninges (Beckmann and Kubie [1]), it became apparent that among the visual symptoms diplopia occurred with surprising frequency. Sometimes the diplopia was explicable by the existence of palsies of the extra-ocular muscles. In a certain number of cases, however, there was neither history nor physical sign of strabismus, ptosis, or pupillary disturbances. Furthermore, where the record furnished sufficient data it was evident that the diplopia was most troublesome when the patient attempted to fix both eyes on an object for precise observation, and that it was not influenced by conjugate deviation of the eyes in any direction (whereas diplopia which results from weakness of any of the muscles of the eye is always altered in some way by conjugate deviation of the eyes).

This type of diplopia had not occurred in any patients with homonymous defects in the visual fields, but only in the presence of bitemporal hemianopia. Theoretically, it could occur in the presence of binasal hemianopia as well, but no examples of this type of field defect occurred among the cases studied. Not all patients with bitemporal hemianopia developed diplopia, however; and a review of the histories made it clear that diplopia occurred only in association with periods of amblyopia. Where the amblyopia was transient, the diplopia was transient; where the amblyopia was permanent, the diplopia persisted. In one case (Case 1), it was our good fortune to watch the development of the double vision, and to see that it occurred when the bitemporal defects in the visual fields had actually invaded the macula. In the other cases presented below, it is possible to deduce a similar progression of the lesion from the data in the histories and in the examinations.

---

[1] Travelling Fellow, Medical Fellowship Board, National Research Council, Washington, D.C.

The conditions necessary for the development of this type of diplopia would seem to be these: (1) heteronymous defects in the visual fields (bitemporal or perhaps binasal); (2) reduction of visual acuity at the maculæ to less than that of the adjacent areas on the relatively normal halves of the retinæ; (3) the power to project the image perceived into space accurately in relation to the point of the retina on which the image falls (i.e., normal central-retinal localization).

Under these conditions the patient attempts to improve his binocular vision by using perimacular fields. If, in so doing, he uses homologous fields, one image will fall upon the amaurotic half of one retina, and he will see with only one eye. The patient, however, can achieve binocular vision by using both normal, heteronymous, juxta-macular fields, but only with the production of diplopia. Naturally, this diplopia, as certain of our patients demonstrated, is itself heteronymous in nature; i.e., the image from the left eye falls to the right of that from the right eye, and *vice versa*. Furthermore, if the defect in the visual fields is bitemporal, the patient will diverge his eyes so as to bring into focus the normal temporal halves of his retinæ, with a resulting divergent strabismus. This condition was observed in some of the cases presented here. Whether divergence of the visual axes becomes visible or not will depend entirely upon how far into the perimacular field the patient is forced or able to go in order to find an area of visual acuity greater than that of the macula itself.

We have been unable to find any reference to this phenomenon in the literature. Further investigation of it must wait upon the accumulation of clinical data from similar cases with more precise quantitative perimetry and scotometry, as well as careful investigation of the reciprocal functions of the external muscles of the eye.

CASE REPORTS.

Out of a group of twenty-one cases of tumour of the hypophyseal stalk, two examples of this type of diplopia are presented here; and six examples from among twenty cases of adenoma of the hypophysis. In several other cases from each of these groups of tumours, and in one case of suprasellar endothelioma, diplopia occurred that seemed definitely to be of the same nature. These cases are not, however, included in the report, either because essential data were not available, or else because there was some uncertainty as to the exact condition of the extra-ocular muscles.

Case 1.—*Walter A., a middle-aged man, after partial extirpation of a tumour of the hypophyseal stalk developed a progressive bitemporal hemianopia. As the progressive defect invaded the macular field, the patient developed diplopia without any extra-ocular motor palsies. As the area of macular defect became more extensive, diplopia became less distinct, the patient seeing instead only the edges of any object on which he attempted to focus both eyes.*

Walter A., an unmarried man, aged 43, was admitted to the service of Dr. Gordon Holmes on October 24, 1928. The history, the physical findings, and the presence of intrasellar opacities in the roentgenograms of the skull led to the diagnosis of a tumour of the hypophyseal stalk. This diagnosis was verified at operation on November 2, 1928. (See Beckmann and Kubie [1], Case 17).

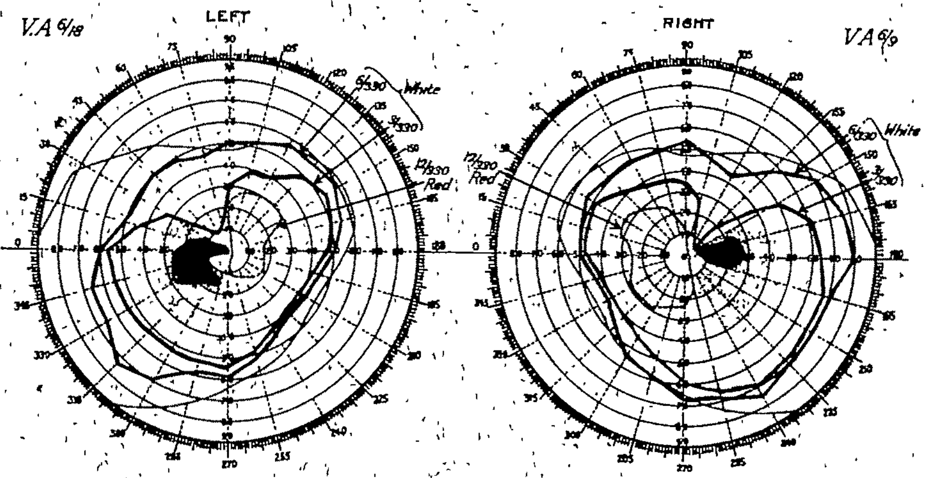


FIG. 1.

Six months earlier the patient had begun to complain of pain and a feeling of pressure in his left eye. For two months this had been relieved by glasses, but then vision in this eye became misty, especially in the outer corner. Gradually the dimness "moved across like a shutter from the left." Only one month before his admission he noticed that his right eye fatigued easily, and that his vision became blurred on reading.

On admission examination of his eyes showed a visual acuity on the right of $\frac{6}{9}$ and on the left of $\frac{6}{18}$. The fundi were normal. There was slight constriction of the temporal field of the right eye, with a defect in the upper temporal quadrant and a cæcal scotoma *that did not involve the fixation point.* In the left eye there was a more marked temporal constriction, a deeper defect in the upper temporal quadrant and a cæco-central scotoma. The red fields showed a complete bitemporal hemianopia (see fig. 1). The external ocular movements were entirely normal and there was no diplopia.

On November 2, 1928, Sir Percy Sargent explored the base of the skull through a right frontal incision. The dorsum sellæ was found to be bulging, and after incision small masses of gelatinous and calcareous material were removed.

After a post-operative period which was complicated by intense meningeal irritation, persistent bronchitis, and delirium, the patient made a fair recovery and was discharged from the hospital on January 9, 1929. At that time his visual acuity was $\frac{6}{12}$ in the right eye and $\frac{6}{18}$ in the left. Both fields were quite full for white and red (see fig. 2). All external ocular movements were normal and there was no diplopia.

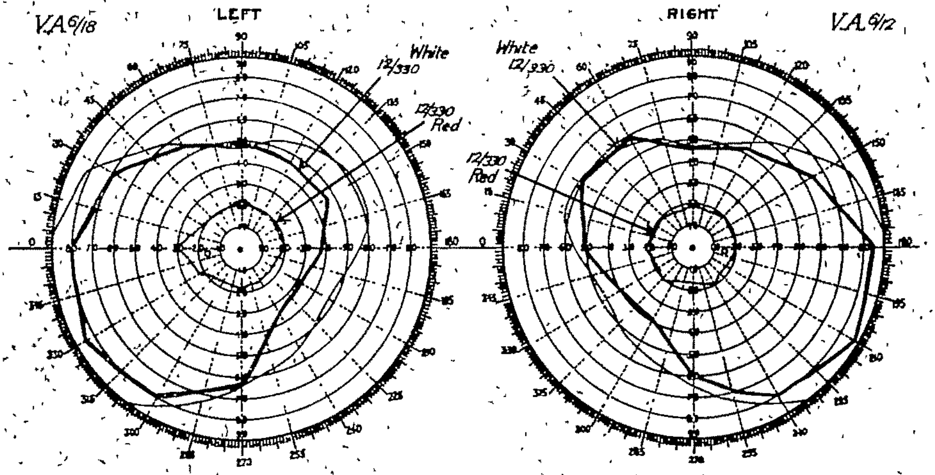


FIG. 2.

On February 8, 1929, the patient returned to the hospital for a re-examination. Visual acuity was $\frac{6}{18}$ in both eyes. The fundi were still quite normal. His only complaint at this time was of intense lancinating pains in the vertex, which usually troubled him in the early morning and then disappeared for the remainder of the day. As before there was no defect demonstrable in the movements of the eyes and there was no diplopia. His visual fields for white and for red are shown in fig. 3. The early bitemporal defect in his visual fields had not yet invaded the macular region of either eye.

Seven weeks later, on March 26, 1929, the patient was examined again. Now, however, he complained of mistiness of vision in the lateral fields, especially in the left eye ("as though a screen of gelatine were before it"), and of diplopia. He volunteered the information that he could read only with his glasses and had difficulty whenever he tried to look directly at an object, because the words or objects seemed to be vaguely doubled. On questioning, it became evident that there was little spreading of the images, that the displacement was not increased by conjugate deviation of the eyes in any direction, and that one image was fuzzy and indistinct. The two images were so close as to be almost superimposed.

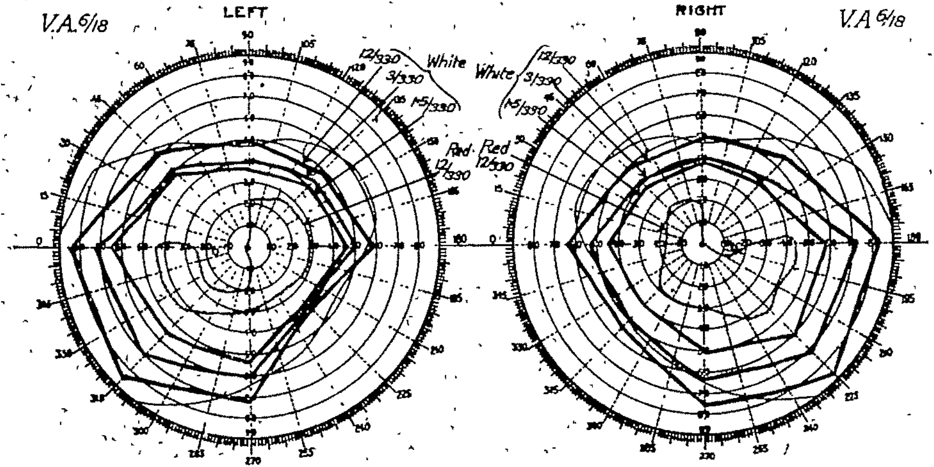


FIG. 3.

On examination, the visual acuity was found to be $\frac{6}{9}$ in the right and $\frac{6}{12}$ in the left eye; but with each eye he read only the letters on the nasal end of the line. The fundi were not changed except for doubtful pallor in the left disc. The visual fields, which are reproduced in fig. 4, showed a bitemporal

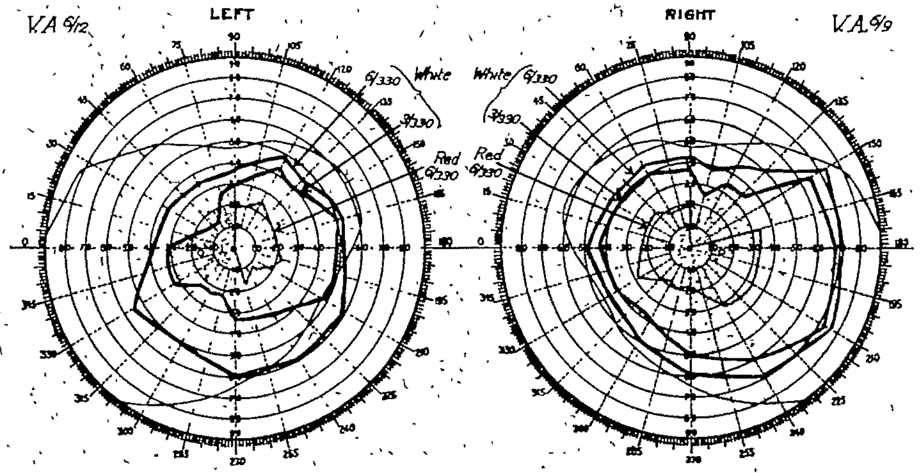


FIG. 4.

relative hemianopia for white and red, over-riding the fixation point by about five degrees. The visual acuity which the patient achieved was due not to the maculæ but to the juxta-macular nasal areas. His diplopia evidently occurred when he focused these two nasal fields upon any point.

On April 15 the patient was seen again. The visual acuity of the juxta-macular nasal fields was still $\frac{6}{9}$; but now the bitemporal hemianopia and the relative central loss had so increased that with either eye the patient could read only the nasal half of the letters at which he looked. He complained that when using both eyes he either saw double or else that he saw only the lateral edges of what he was looking at (i.e., the crossed nasal fields did not meet each other in the mid-line). His visual fields are reproduced in fig. 5. Again there was no weakness of any of the extra-ocular muscles.

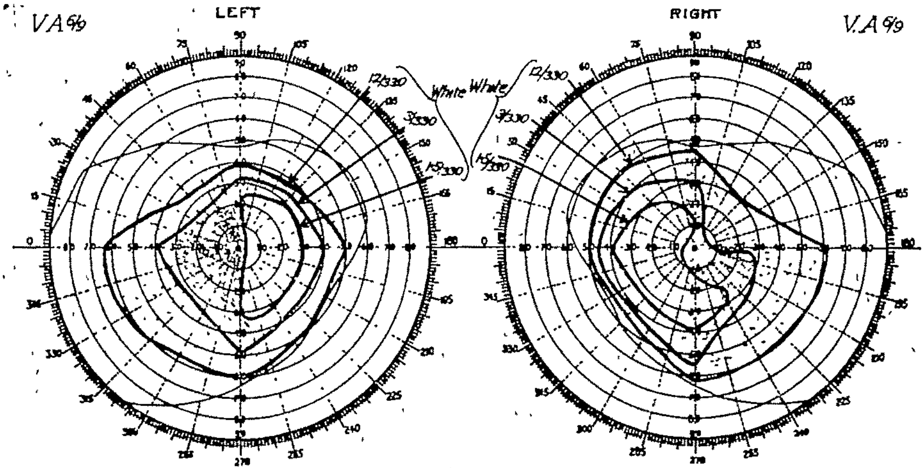


FIG. 5

Case 2.—James W., an elderly man, had coincident diplopia, amblyopia, and bitemporal hemianopia, without extra-ocular motor palsies. The exact relationship of macular to perimacular acuity was not studied; but there is strong presumptive evidence that macular acuity was less than that of the juxta-macular nasal fields. The bitemporal hemianopia and presumptive macular defect had given rise to a slight divergent strabismus. The diplopia was heteronymous, proving that the images fell upon the nasal fields.

James W., a married man, aged 60, was admitted to the service of Dr. Gordon Holmes on August 26, 1924. The history and the physical findings led to the diagnosis of a non-acromegalic adenoma of the hypophysis; a diagnosis which was confirmed at operation two months later.

About five years before his admission to the hospital the patient had experienced some transient difficulty with his eyesight, which was relieved by glasses. Two years later, however, the difficulty had recurred and persisted. At this time he complained that his vision was not clear, but "as if smoke were floating before my eyes." This began in the left eye, but later involved the right as well; and when this occurred diplopia made its appearance. He could recall that almost from the first the images were on the same level and upright, seeming to him to be an inch or so apart. Closing the left eye made the right-hand image disappear; and it was this right-hand image which was the less distinct (which is consistent with the earlier involvement and the more serious deterioration of vision in the left eye). To read, he had to close the left eye

At this time he was examined in a hospital in Birmingham, and the report stated that visual acuity in the right eye was $\frac{6}{12}$, and in the left eye $\frac{6}{60}$ There was bilateral optic atrophy, and a bitemporal hemianopia. The external ocular movements were normal, despite the diplopia No data were given as to the relation of macular to juxta-macular acuity; but his occasional complaints of the appearance of floating balls of light directly in front of him are suggestive of a macular disturbance.

On examination in the National Hospital, two years later, visual acuity in the right eye had dropped to $\frac{6}{24}$ and in the left eye to $\frac{3}{24}$. Mr Williamson-Noble reported greyish-white pallor of both discs, more marked in the left eye The visual fields for white are reproduced in fig. 6. Unfortunately they are purely qualitative, and show a bitemporal hemianopia which bisects the fixation point but fail to give any exact idea of the relative acuity of macular and perimacular vision. It was noted, however, that even with the better eye (the right), the patient had difficulty in keeping his place on a line of print, which is most readily understood on the basis of a foveal defect with a resulting tendency for the eye to wobble from one perimacular field to another (*v.i.* Discussion).

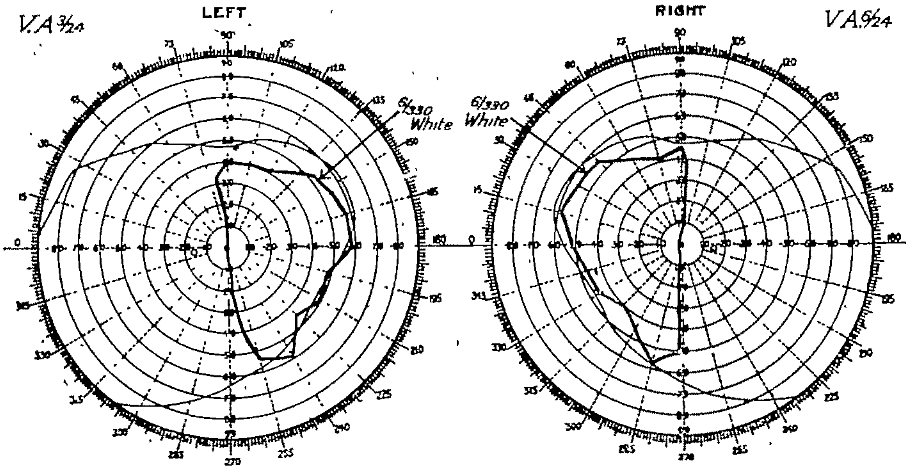


FIG. 6

External ocular movements were found to be normal in all directions. Nevertheless there was a slight external strabismus, especially of the right eye, which is in keeping with the bitemporal field defect and the better acuity of the right eye.

On examination of the diplopia, it was found that the images were parallel, the left one sometimes slightly higher than the right, and disappeared on closing the right eye; whereas the right-hand image disappeared when the left eye was closed. The images must, therefore, have arisen from the two nasal fields.

Case 3.—*Florence S*, *a woman aged* 50, *after suffering from bitemporal hemianopia for some months, developed marked amblyopia and diplopia during a transient period of defective macular vision. When examined, some months later, the remains of the central defect were demonstrable in one eye; but the condition of the other eye could be deduced only from the history. The persistent bitemporal defect caused convergence to be poorly maintained.*

Florence S, an unmarried woman, aged 50, was admitted to the service of Dr. Gordon Holmes on November 6, 1924. Her history and the physical findings led to the diagnosis of a non-acromegalic adenoma of the hypophysis, a diagnosis which was verified at operation on November 15.

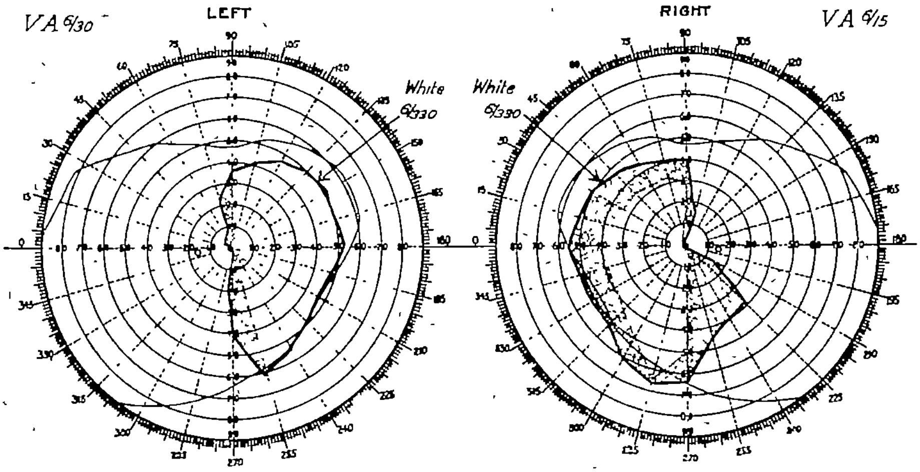


FIG 7

Almost three years before her admission to the hospital the patient had suffered from some ill-defined visual difficulty which had apparently been relieved by the use of glasses. Some months later, however, she noticed that she could not see well to either side. Again her symptoms decreased for several months, this time during a course of endocrine therapy. One year before her admission, however, there was a sharp reduction of visual acuity, and shortly thereafter diplopia appeared for a time. Again vision improved during a period of glandular feeding, to such a point that the patient could read quite comfortably. Finally, however, two months before she was examined in the hospital, acuity decreased and a marked bitemporal defect became manifest.

In the hospital, the visual acuity of the right eye was found to be $\frac{6}{15}$. That of the left eye is recorded as $\frac{6}{30}$, but at the same time a note is made that the letters flickered in and out of vision, so that one must conclude that macular vision was less than that of some adjacent perimacular area. Mr. Paton reported that both discs showed temporal pallor, more marked in the left than in the right eye. The visual fields are reproduced in fig. 7 There is a bitemporal hemianopia, in the right eye apparently just reaching the fixation point, and in the left eye probably over-riding it (presumably the remains of what according to the history must have been a definite central defect).

The external ocular movements were full, synchronous and steady in all directions, except that convergence was poorly maintained, which is consistent with the bitemporal and central defects. Macular vision had so far recovered, at this time, that the only diplopia observed was a doubtful "occasional diplopia on looking at distant objects far to the right."

Case 4.—Dr. K. M, an elderly physician, had diplopia which was not referable to weakness of any external ocular muscles, associated with a bitemporal hemianopia and defective macular vision. With improvement in macular vision the diplopia ceased, despite the persistence of the bitemporal hemianopia.

Dr. K. M., a married man, aged 61, was examined by Dr. Gordon Holmes on January 1, 1927. The history and the physical findings led to the diagnosis of an intrasellar or suprasellar neoplasm. At operation, five weeks later, an adenoma of the hypophysis was found and histologically verified.

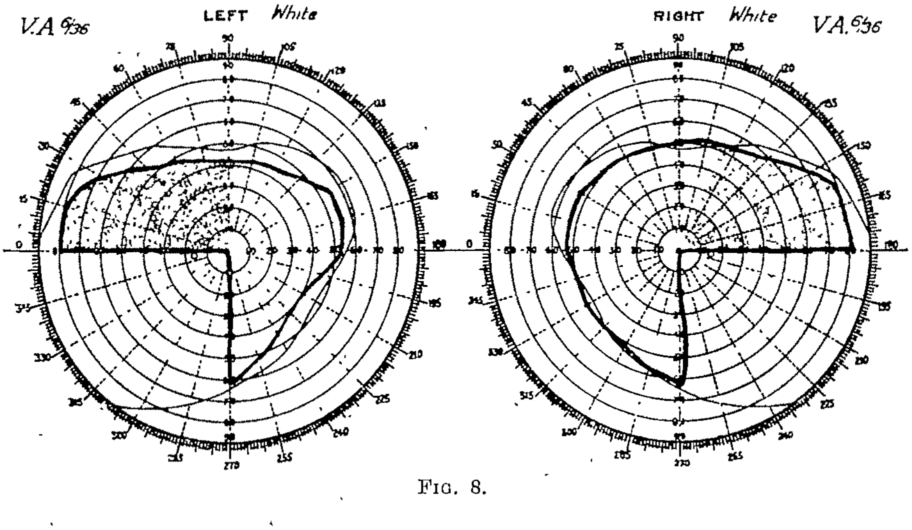


FIG. 8.

When examined by Dr. Holmes the patient had no diplopia, and no weakness of the external ocular muscles. The visual fields showed a bitemporal loss which spared the fixation point so completely that visual acuity was $\frac{6}{6}$ in the right eye and $\frac{6}{18}$ in the left. Both discs were pale, however, and the history, and the charts of previous perimetric examinations, which the patient brought with him, indicated that there had been earlier periods of more extensive visual defect.

Three years before coming to Dr. Holmes the patient had had vague visual difficulties, and after these had existed for twelve months diplopia developed. Despite the fact that the patient was a physician and could give a very accurate story, the description of the diplopia did not point to a weakness of any of the external ocular muscles. In addition to the diplopia there was a definite history both of a macular and of a temporal defect in each eye, since the patient could see only the nasal half of an object at which he looked, and in trying to read he had to lay a straight edge under the line which he was following in order to keep his place. As further evidence of the existence of a macular defect at this time is the fact that the question was raised among the ophthalmologists whom he had consulted as to whether he might have perimacular hæmorrhages This was finally denied. At that time visual acuity was about $\frac{6}{36}$. The visual fields recorded during this period are reproduced in fig. 8, and show a complete inferior temporal loss in both fields, with a relative superior temporal amblyopia. The exact condition of macular vision is not made clear by these purely qualitative fields. Later fields demonstrate a gradual progression to a practically complete bitemporal hemianopia, but the history and examination show that, synchronously with this, macular vision (and visual acuity) improved, and as a result the diplopia disappeared (fig 9)

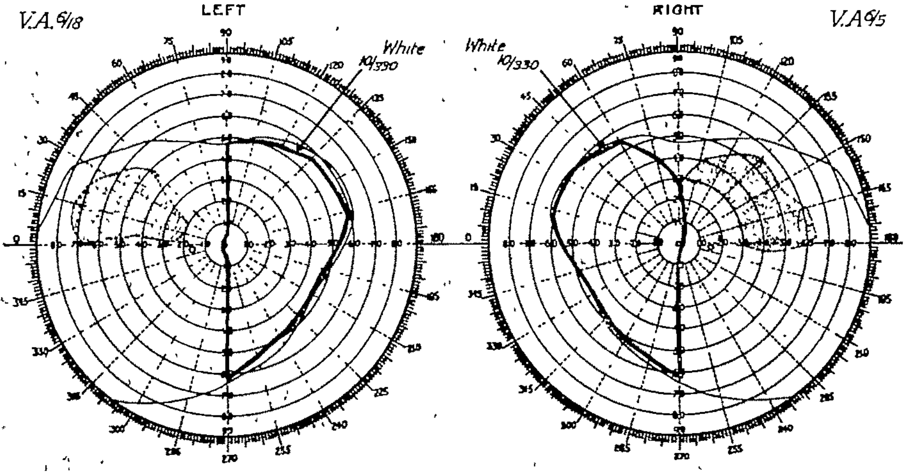


FIG. 9.

Case 5.—Louisa N , a young woman, was seen after several years of progressive deterioration of vision associated with diplopia. There was no extra-ocular motor palsy. Vision was lost except in the upper nasal quadrant of each eye. The patient could produce diplopia at will by attempting to focus these two fields upon a bright light.

Louisa N., an unmarried woman, aged 27, was admitted to the service of Dr. W. J. Adie on December 1, 1925. The history and the physical findings pointed to the presence of a suprasellar neoplasm, and some weeks later a typical adamantinomatous cyst of the hypophyseal stalk was exposed at operation. (See Beckmann and Kubie [1] Case 9.)

Visual difficulties had begun insidiously about ten years before her admission to the hospital. Of their exact nature little is known. Amblyopia had affected the right eye first, but then had improved in this eye, only to appear in the left eye, where it progressed rapidly almost to blindness. Eventually vision deteriorated in the right eye as well. At some time, during the development of this condition, diplopia had appeared; but for one year prior to her admission spontaneous double vision had ceased. It was noted, however, that the patient could still "cause diplopia on voluntary effort" (i.e., with the effort to use binocular vision).

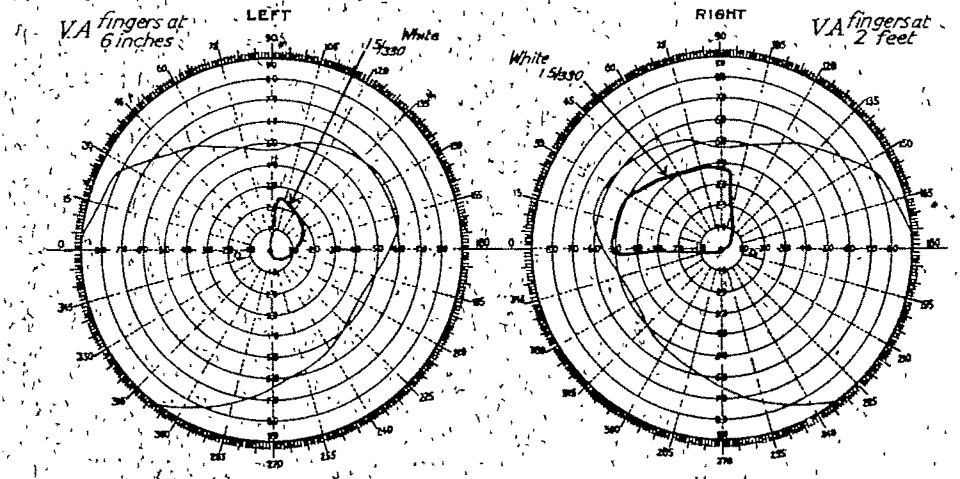


FIG. 10.

On examination it was found that central acuity was reduced to counting fingers, at 6 in. in the left eye, and at 2 ft. in the right. Mr. Williamson-Noble reported that both discs were pale, with sharply-defined edges, clear laminæ cribrosæ, and normal vessels. The visual fields are reproduced in fig. 10. They demonstrate the persistence of an island of imperfect vision in the upper nasal quadrant of each eye. The relationship of macular to perimacular acuity within these islands is not shown.

All external ocular movements were full, steady, and synchronous in all directions. Nevertheless, it was noted that she had diplopia when concentrating on a light in any direction except to the left (where it passed out of the field of vision of the left eye completely).

Case 6.—Edie A. W., an elderly woman, suffered from persistent diplopia and amblyopia. The history does not furnish full details of the development of the condition. There was an extensive temporal defect in one eye which *included the fixation point; and a deep upper temporal quadrantic defect in the other with an absolute cæco-central scotoma. There was no extra-ocular motor-palsy.*

Edie A. W., an unmarried woman, aged 57, was admitted to the service of Dr. Gordon Holmes on May 21, 1926. The history and the findings led to the diagnosis of an adenoma of the hypophysis without acromegaly, and at operation, one month later, this diagnosis was verified.

Vaguely for ten years, and more insistently and definitely for five years, the patient had suffered from diplopia. This occurred chiefly during efforts to use her eyes for fine work. She said that, "Words would drop and get out of place; numbers would get mixed up." She was not aware, subjectively, of any temporal loss. The doubled images sometimes seemed to be side-by-side and close together. Three years before her admission the reduction in acuity became more noticeable, with progressive inability to read, and pain in the eyes and burning headaches. Beyond this the history furnishes no details

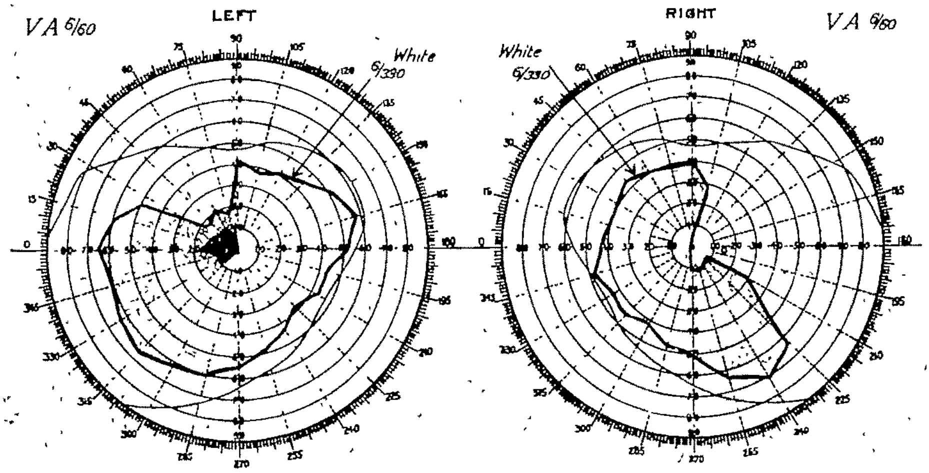


FIG. 11.

On examination, her visual acuity was found to be reduced to $\frac{6}{60}$ in both eyes. Mr Williamson-Noble reported that there was general pallor of both discs, more marked in the left eye. The fields are reproduced in fig. 11. In the right eye there was a deep defect in the upper temporal quadrant which included the fixation point and invaded the inferior temporal field In the field of the left eye the absolute defect in the upper temporal quadrant was less extensive, but the relative dimness involved most of the temporal field, and in addition there was a small, absolute cæco-central scotoma.

All external ocular movements were full, steady and synchronous. For this reason the story of diplopia was discounted and no close scrutiny or examination of the condition was made.

Case 7.—Dorothy M., a young woman, passed through periods of recurrent and deepening amblyopia, with loss first of the left temporal field and then of the right. After an episode of scintillating central scotoma, colour vision and central acuity became dim, and diplopia developed, without extra-ocular motor palsies. With recovery of central vision the diplopia disappeared, despite the persistence of a bitemporal hemianopia.

Dorothy M., an unmarried girl, aged 18, was admitted to the service of Dr. Gordon Holmes on June 15, 1927. The history and physical findings led to a diagnosis of a non-acromegalic adenoma of the hypophysis. On July 4 this diagnosis was confirmed at operation.

Five months before admission she noticed that after reading for any length of time her vision blurred. The left eye was more seriously involved than the right; and within a day or so she began to experience difficulty in seeing objects to her left. At the same time headaches, from which she had suffered for some months, became worse and were accompanied by flashes of blue light which appeared in one eye at a time, more often in the left than in the right.

Six weeks after the onset she developed definite difficulty in seeing things that were on her right side, and there was marked reduction in the acuity of her colour vision. Within a few weeks after this she began to notice that she was seeing double. This was almost continuous for two weeks, then became intermittent, and finally disappeared several weeks before she entered the hospital. No exact analysis of the relationship of the images was obtainable

In the hospital, the visual acuity was found to be $\frac{6}{18}$ in the right eye and $\frac{6}{9}$ in the left. The charts of the visual fields before operation are incomplete, but rough tests, carefully done, revealed a bitemporal hemianopia. Macular vision was more acute than perimacular vision, objects suddenly becoming clearer at the fixation point. The right fundus was found to be normal by Mr. Paton, but the left showed temporal pallor of the optic disc.

There was no diplopia at this time, and the third, fourth and sixth nerves showed no abnormality.

The disappearance of the diplopia, despite the persistence of the bitemporal hemianopia, is easily explained by the marked improvement in macular acuity, especially in the left eye.

Case 8.—Annie H., an elderly woman, had progressive dimness of vision, and then diplopia without weakness of the extra-ocular muscles. The diplopia was most evident on efforts to read. Loss of temporal fields was noted early on one side; but was not observed by the patient in the other eye until vision in the first had almost gone. In this case the coincidence of the bitemporal hemianopia and the reduction of macular vision with the appearance of the diplopia is only presumptive, from the history, since the patient first came for examination three years after one eye was quite blind. All extra-ocular movements were normal; but the long-standing bitemporal defect had caused a slight divergent strabismus.

Annie H., a married woman, aged 50, was admitted to the service of

Dr. S. A. Kinnier Wilson on January 30, 1922. The history and the physical findings pointed to the existence of an adenoma of the hypophysis without acromegaly. This diagnosis was verified at operation and autopsy a few weeks later.

For several years the patient had suffered from progressive dimness of vision At first distant objects were difficult to see; then diplopia appeared. The patient claimed that in a word of three letters, such as "MEN," the middle letter "E" would be seen doubled. Or two men approaching her in the street might appear as three. The third image was always indistinctly superimposed upon the other two, and she could not tell "which man had been doubled." At times the last word in a line of print might seem to be on a higher level than the rest of the words.

At about the same time, or immediately after the onset of this diplopia, the patient first became aware of the loss of her temporal fields, especially on the left side. It was not until the left eye became quite blind, however, three years before her admission, that she became fully aware of the temporal loss on her right side. With the blindness of her left eye the diplopia had disappeared.

On examination, the blindness of the left eye was confirmed; and visual acuity of the right eye was found to be reduced to $\frac{6}{60}$. There was a complete right temporal hemianopia, to rough tests, passing vertically through the fixation point.

No charts of this condition are found in the record. Mr. Paton reported that both discs were quite white, with clear edges.

There was a slight but definite divergent squint, quite compatible with the bitemporal field defects which had existed in both eyes and which persisted in the seeing eye. All external ocular movements were full, steady, and synchronous, however.

DISCUSSION.

In binocular vision the fusion of images formed in the two eyes depends upon the use of corresponding points of the two retinæ. If anything occurs to alter the normal synergic movements of the two eyes, so that the portion of the retina of one eye on which the image falls is not homologous with that of the other, diplopia results. Hitherto, there has been only one recognized cause for such a failure of the two eyes to work together, i.e., a palsy of one or more of the extra-ocular muscles. In the cases described in this report, however, repeated instances are given of diplopia occurring without there being any weakness of the eye muscles. On the contrary, the diplopia seems to result from the attempt of the normal extra-ocular muscles to compensate for defects in the visual fields and in macular acuity by deliberately bringing into simultaneous use portions of the retinæ which had hitherto been unassociated.

The mechanism of this type of diplopia is allied to the phenomena which are observed in coal-miners' nystagmus. This is a condition which occurs in men who have worked for many years in coal mines in which the illumination is so dim that in the dark-adapted eye the visual acuity is greater in the perimacular region than at the macula itself (Medical Research Council: First Report of the Miners' Nystagmus Committee, 1922 [4]; Llewellyn [3]). As a result the eye of the miner comes to depend upon perimacular rather than macular vision. But since there is no single spot in the perimacular retina, the visual acuity of which is greater than all the rest, and since the perimacular retina is subject to rapid fatigue, a tendency arises to roll the eyes frequently from one point of temporary fixation to another. (Cridland [2] suggests, on p. 701, further data on this tendency which is not, however, relevant to our problem.) It must be emphasized that in the absence of defects in the visual fields or of extra-ocular motor palsies, the eyes move with parallel axes. Therefore in uncomplicated cases of miners' nystagmus homologous parts of the retinæ are always in use and no diplopia occurs. Llewellyn [3] could find but two cases of diplopia in 600 instances of this disease, and believes these to have been the result of extraneous factors.

In the cases reported here it was not poor illumination, but damage to the macular bundle, which lowered the visual acuity of the macula below that of the surrounding retina. The result was similar, in that clearer vision was sought by using perimacular fields. But unlike the sufferers from miners' nystagmus these patients could not use homologous parts of their retinæ because of the bitemporal defects in their visual fields. Diplopia from the use of heteronymous fields was therefore inevitable.

On the other hand, closely analogous to the oscillations of the eyes in miners' nystagmus was the complaint of some of our patients that the double images "wobbled." Cases 2 and 4 could not keep their eyes focused on a line of print without laying a straight ruler to guide them. Case 6 was troubled because "words would drop and get out of place; numbers would get mixed up." Case 8 observed that the relative positions of the two images would keep shifting.

This type of diplopia was actually observed and examined only in Cases 1, 2 and 5. In Case 1 the patient was watched through the successive stages of a rapidly advancing bitemporal defect; and it was seen that diplopia developed without weakness of any extra-ocular muscles, only as the macular areas of both eyes were encroached upon.

This condition persisted for two weeks, and then progressive failure of vision eliminated the diplopia.

In Case 2 it was possible to prove that the double images arose from the two nasal fields, since the diplopia was heteronymous and the temporal fields were blind. This fact fully explains the existence of a slight divergent strabismus; because this position would bring into simultaneous use the two temporal retinæ (i.e., nasal fields).

Case 5 affords, perhaps, the clearest evidence of any that our interpretation of this diplopia is correct. This patient was almost blind, except for islands of partial vision in both upper nasal quadrants. When the eyes were relaxed there was no diplopia. But whenever the patient deliberately attempted to focus both eyes on a bright light diplopia occurred at once, demonstrating that under these conditions the normal synergic patterns of the eye movements can be supplanted by voluntary divergence of the visual axes, so as to bring into play both nasal fields for binocular vision. By this divergence of the visual axes areas of greater acuity could be used and binocular vision was achieved; but because heteronymous visual fields were employed a crossed diplopia resulted.

In Cases 3, 4, 6, and 7 the period of diplopia had passed before the patient came under observation; but in each case the history and the residual findings were reasonably convincing that the patient has gone through a stage of bitemporal hemianopia with reduction of acuity at the maculæ. Case 8 is presumably an example of the same condition, but here the history is not entirely complete, and the patient was blind in one eye and nearly blind in the other when she came under observation.

SUMMARY.

(1) The occurrence of true diplopia without any weakness of the extra-ocular muscles is described in six cases of adenoma of the hypophysis and two cases of tumour of the hypophyseal stalk.

(2) In all of these cases there was a bitemporal hemianopia; in none of them was there an homonymous type of defect in the visual fields

(3) In some of the cases it was possible to demonstrate, and in others it was possible to infer from the histories, that visual acuity at the macula was less than that of the juxta-macular nasal field (i.e., the temporal retina).

(4) In certain cases it was clear that the diplopia was heteronymous, the images evidently arising from the nasal fields. In other cases the

images were too close together, or too indistinct, to permit of such exact analysis.

(5) In no case was the diplopia increased by conjugate deviation of the eyes; but rather by efforts to focus both eyes for clearer binocular vision in any direction.

(6) The diplopia must depend, therefore, upon the fact that in the presence of impaired macular vision the patient attempts to use the adjacent areas of the retina in which visual acuity is greater. Since there is a co-existent bitemporal hemianopia, however, the only available fields are the two nasal fields. To secure binocular vision of good acuity he must employ these. Since, however, these are not homologous parts of the retina, diplopia inevitably results. In order to bring into focus his two nasal fields, he must to some extent diverge his visual axes. Whether this divergence will be visible or not will depend upon how far into the perimacular field he must go to find greater visual acuity.

(7) In keeping with this interpretation, certain of the cases showed a slight divergent strabismus without any accompanying weakness of convergence or of internal rotation of either eye on conjugate lateral movements.

It is a privilege to express our gratitude to Dr. Gordon Holmes for his advice in the preparation of this report. We wish, further, to thank the Medical Committee of the National Hospital for their permission to use the records of the cases included here.

BIBLIOGRAPHY.

[1] BECKMANN, J. W., and KUBIE, L. S. "A Clinical Study of Twenty-one Cases of Tumour of the Hypophyseal Stalk," *Brain*, 1929, **52**, 127.

[2] CRIDLAND, B. "Coal Miners' Nystagmus," *Opthalmoscope*, 1912, **10**, 699.

[3] LLEWELLYN, T. L. "Miners' Nystagmus," The Colliery Guardian Company Ltd., London, 1912.

[4] Medical Research Council. First Report of the Miners' Nystagmus Committee, London: H. M. Stationery Office, 1922.

STUDIES ON THE OPTIC THALAMUS OF THE INSECTIVORA.—THE ANTERIOR NUCLEI.

BY W. E. LE GROS CLARK, D.Sc.

INTRODUCTION.

IN a recent paper [8] dealing with the study of the thalamus in the tree-shrew, a primitive and generalized insectivore, it was emphasized that the comparative study of the mammalian thalamus and the homologization of the various thalamic nuclei which have been described are rendered very difficult partly because of the lack of sufficiently detailed accounts of the structure of the thalamus in the different mammalian groups. The development and differentiation of these nuclei show a very considerable degree of variation in different groups of mammals, and this is so even within the limits of a relatively small group of simple animals such as the insectivora. For a comparative study of the thalamus, the brains of the insectivora are especially useful They are small, relatively generalized brains, and readily comparable in their size. At the same time they show marked specific characteristics in which they contrast with each other. Such a differential development of the cerebrum as a whole is reflected to a large extent in the structure of the thalamus, and it seems feasible to surmise that a comparative study of these brains may yield evidence of an anatomical nature concerning the significance of the different thalamic nuclei.

Of the nuclear masses which make up the thalamus, the anterior group of nuclei can usually be fairly readily distinguished and identified. But the wide variation in the relative degree of development of its several elements may give rise to considerable difficulties. It will be well here to anticipate the subsequent discussion of the observations which have been made, and to define the anterior nuclei of the thalamus as those groups of cells situated in the antero-dorsal region of the thalamus, and in connection with which the fibres of the mammillothalamic tract (bundle of Vicq d'Azyr) terminate. This definition may be regarded as holding even though in some mammals in which one of the elements is relatively poorly developed it may not be possible by ordinary methods actually to trace the terminal fibres of this tract into it. Three elements of the group are recognized, and each of them, when well developed, is found to receive mammillothalamic terminals. The three elements, with their synonyms, are as follows, using the nomenclature adopted by Gurdjian [10] in his work on the diencephalon of the rat:—

Nucleus anterodorsalis (angular nucleus of Cajal, n. anterior C of Monakow and others, n. anterior B of Winkler and Fortuyn, n. triqueter of Livini and Rothig, n. disseminatus of Sachs, Brunner and Spiegel, and Woollard, n. dorsomedialis of Papez, ? part of n. reuniens of Malone).

Nucleus anteroventralis (dorsal nucleus of Cajal, n. anterior A of Monakow, Winkler, Fortuyn and others, n. anterior of Papez, Pines and others, n. dorsalis magnus of Sachs and others).

Nucleus anteromedialis (included among the medial group of nuclei by most authors).

MATERIAL AND METHODS.

The brains of four species of insectivora have been used for the study of the thalamus. The characteristics of these brains have been described elsewhere [5, 6, 7], but the salient features which distinguish them may be briefly indicated (fig. 1).

Erinaceus europæus (hedgehog).—The primary and secondary olfactory centres of the brain are very well developed, especially the olfactory bulb and the piriform lobe. The dentate gyrus is conspicuous and forms a convoluted strip of cortex on the medial surface of the cerebrum. The corpus callosum is small and of primitive type, while the ventral commissure is relatively large. The neopallium forms but a small proportion of the cortical surface. The optic nerves are very small and the visual cortex poorly differentiated.

Macroscelides (elephant-shrew).—The olfactory bulb and the piriform lobe are relatively smaller, though quite well developed. The hippocampus shows an extraordinary development, especially the subsplenial portion, and out of all proportion to the secondary olfactory centres. This enlargement of the hippocampus has led to a distortion of the neopallial and hippocampal commissures. The corpus callosum has become stretched out to form a long, attenuated commissure, and is clearly separated from the fornix commissure which, in section, assumes the crescentic form characteristic of marsupial brains. The optic nerve is large, and the anterior colliculus enormous. The visual area of the cortex, however, is poorly differentiated. The retrosplenial area of the cortex, which in most mammalian brains is limited to a small area in relation to the splenium of the corpus callosum, extends over a considerable area and reaches on to the dorsal surface of the neopallium.

Ptilocercus lowii (pen-tailed tree-shrew).—This is a generalized brain showing a moderate development of the olfactory bulb and piriform lobe. The hippocampal formation is also moderately developed, and shows a well-marked subsplenial flexure. The corpus callosum is elongated, and the ventral commissure is small.

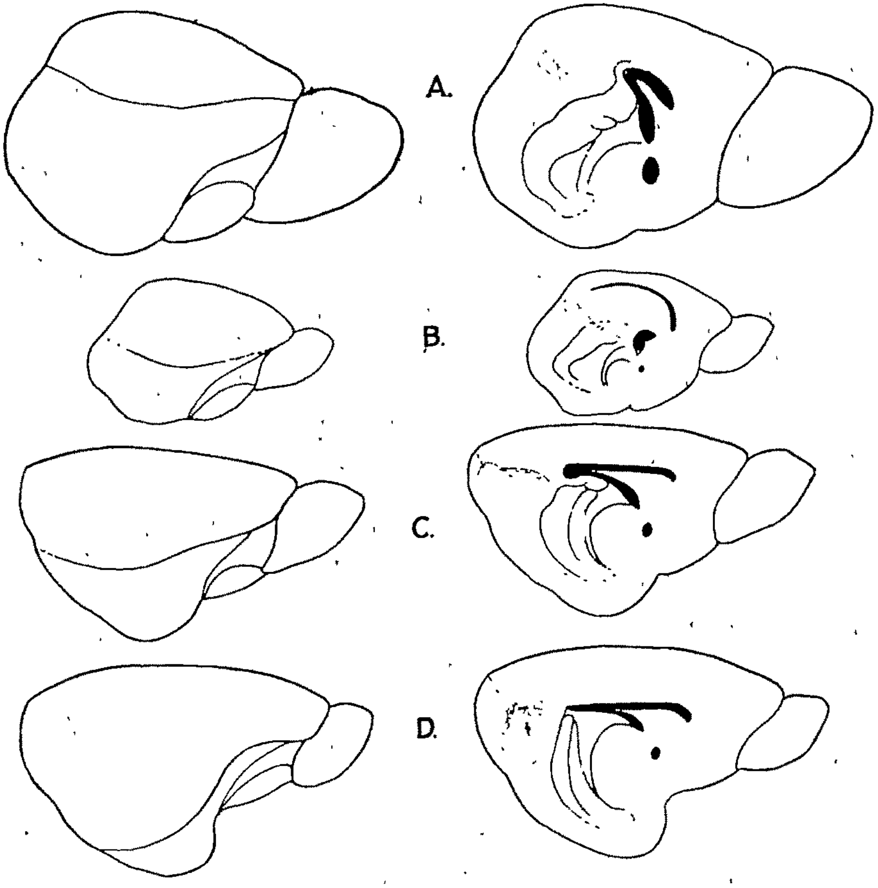


Fig. 1.—Lateral and medial views of the brains of four species of insectivores. (*a*) *Erinaceus.* (*b*) *Macroscelides.* (*c*) *Ptilocercus.* (*d*) *Tupaia minor.* (× 2½.)

Tupaia minor (lesser tree-shrew).—In this brain there is a diminution of the olfactory bulb and piriform lobe. A reduction of the hippocampal formation is also indicated by the absence of any subsplenial flexure. The corpus callosum is elongated and shows no splenial thickening, the ventral commissure is small and the fornix commissure somewhat reduced in comparison with the other insectivore brains. The neopallium is much better developed and forms definite occipital and temporal poles. The optic nerve is large, and the anterior colliculus is very large, especially in comparison with the reduced size of the posterior colliculus. Unlike the other brains, the visual cortex is well differentiated and extensive. There is also an indication of the sulcus calcarinus.

The thalamus has been studied by series of coronal sections, and in the case of *Erinaceus* with sagittal sections also, one or more series of each being stained with toluidin blue, and one with iron-hæmatoxylin. The latter series are of considerable aid in the interpretation of the cyto-architecture of the thalamus and allow the relations of the thalamic nuclei to the main fibre tracts to be studied. It is clearly not possible, however, by these methods to give a detailed and finished account of the whole of the fibre connections of the nuclear groups.

In the descriptive account, planes have been indicated in an antero-posterior direction by giving the numbers of the sections. These sections have been numbered from before backwards, the first section being taken as that in which the anterior nucleus first appears rostrally. In order to give a correct impression of the anteroposterior extent of the thalamus, below are tabulated the number of sections of each series from which the descriptions have been given from Section 1, as far caudally as the anterior limit of the posterior commissure, together with the thickness at which the sections were cut:—

Erinaceus.—61 sections at 15μ, every fourth section mounted.

Macroscelides.—107 sections at 15μ, every section mounted.

Ptilocercus.—157 sections at 15μ, every section mounted.

Tupaia minor.—123 sections at 12μ, every alternate section mounted.

TEXT FIGURE ABBREVIATIONS:

Ad	N. anterodorsalis	M T	Tractus mammillothalamicus
Am	N. anteromedialis	N R	Nucleus reticularis
Av	N. anteroventralis	O C	Optic chiasma
A C	Anterior colliculus	O H	Tractus olfactohabenularis
C Ad	Commissura interantero dorsalis	O T	Optic tract
Dm	N. dorsomedialis	P C	Posterior colliculus
F	Fornix	P C M	Pedunculus corporis mammillaris
F R	Fasciculus retroflexus	Re	N. reuniens
G C	Commissure of Ganser	S M	Stria medullaris
H	N. habenulæ	Va	Anterior ventral nucleus
L	N. lateralis (pars anterior)	Vp	Posterior ventral nucleus
L G	Lateral geniculate body	V C	Ventral commissure
M G	Medial geniculate body		

Tupaia minor. (Fig. 2.)

The elements of the anterior group of nuclei in the thalamus of this animal can readily be homologized on the basis of cyto-architecture with those which have been described in other mammals.

The *anterodorsal nucleus* is conspicuous for the fact that its constituent cells are closely packed together and are more darkly stained in toluidin blue sections than those of the other nuclei. The cells are rounded, oval, and subangular, rather smaller towards the anterior end and the lateral part of the nucleus than elsewhere, and not larger than those of the anteroventral nucleus. The nucleus first becomes evident in this series of transverse sections when traced cranio-caudally at about

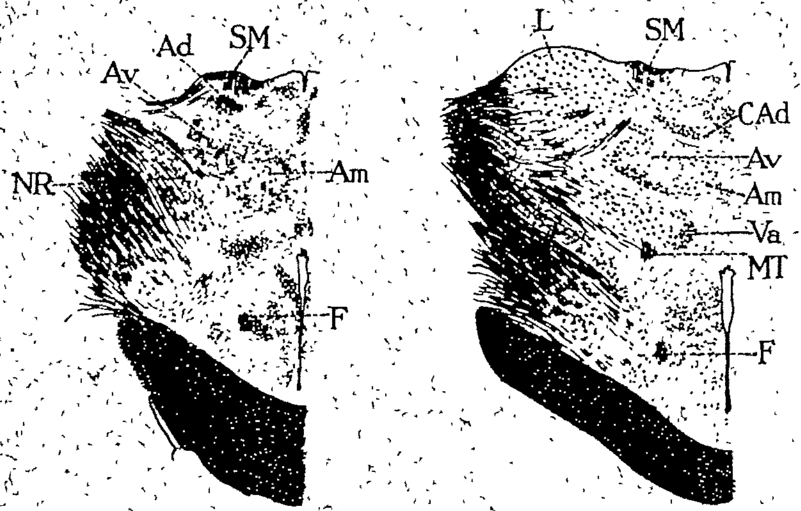


FIG. 2.—Coronal sections (28 and 38) of the thalamus of *Tupaia minor*. (× 10½.)

section 18, where it forms a narrow crescentic cap covering the upper surface of the ventral element. Here it lies immediately subjacent to the stria medullaris and extends inwards towards the nucleus parataenialis. The long axes of the oval cells are usually disposed concentrically with the circular anteroventral nucleus. By section 25, its medially-placed cells show a tendency to drift towards the median plane preparatory to the formation, in a slightly more caudal plane, of a commissural nucleus, and here it comes into relation laterally with the anterior extremity of the lateral thalamic nucleus (nucleus lateralis A). By section 30, it forms an oblique band of cells reaching dorsolaterally almost to the dorsal surface of the thalamus and extending ventromedially towards the median line. It now rapidly diminishes in size. Some few of the characteristic cells of the nucleus may be seen extending across the midline to form a bed nucleus for the interanterodorsal commissure but by section 40 all recognizable trace of this has disappeared. Throughout its extent, the anterodorsal nucleus is richly permeated with bundles of medullated fibres passing up to the stria medullaris, and it may be here noted that this intimate topographical relation of the nucleus with this fibre tract is a very characteristic feature to be found in the other forms examined. Laterally the nucleus is reached by contributions from the superior thalamic radiations.

The *anteroventral nucleus* appears in advance of the previously described element in these sections. At its anterior extremity it is bounded dorsally by the stria medullaris and ventrolaterally by the nucleus reticularis. The nucleus is composed of cells of a type similar to those of the dorsal element, except that they are not so darkly stained and, also, they are much more scattered in their arrangement. In many toluidin blue sections it is impossible to separate the anteroventral from the anteromedial nucleus, especially rostrally. In myelin-stained sections, however, the distinction is clearer. The nucleus is penetrated on its lateral aspect by contributions from the superior thalamic radiations, and many of these fibres tend to encapsulate the nucleus by flowing round its periphery. The lateral olfactohabenular fibres, on their way dorsalwards to join the stria medullaris, further add to this encapsulating effect and thus help to define the outline of the nucleus. The anteroventral element reaches its maximum size in transverse section between sections 25 and 30, and, a few sections more caudally, it blends with the anteromedial nucleus and loses its individuality. In the ventrolateral region of the nucleus, the component cells where they lie up against the internal capsule are rather smaller than elsewhere. Here, also, they are more oval in shape with a tendency to be disposed with their long axes directed medioventrally, evidently in association with commissural fibres of the anteroventral and lateral nuclei. In sagittal sections, the anteroventral nucleus is well defined by the termination of the mammillothalamic tract and in this plane it is also circular in shape.

The *anteromedial nucleus* is hardly to be defined in myelin stained sections. On the basis of cytoarchitecture, however, it can be recognized with little difficulty, though, as stated above, in many sections it runs without interruption into the anteroventral element. Its constituent cells are quite similar to those of the anteroventral nucleus. Rostrally, the nucleus does not extend to the midline. Caudally, it extends medially and meets its fellow of the opposite side at about section 40. Thereafter, it rapidly disappears.

The *mammillothalamic tract* can be readily followed throughout its course in the transverse and sagittal (fig. 9) series of sections. In the latter it is seen to be a long drawn-out tract of even width running first dorsally and then bowed forward by the anterior convexity of the ventral group of nuclei. It terminates mainly in connection with the anteroventral nucleus. Some of its medial fibres, however, can be traced into ultimate relation with the anteromedial element. No fibres of the tract could be demonstrated actually to reach the anterodorsal nucleus.

Ptilocercus. (Fig. 3.)

In this tree-shrew, the anterior nuclei are readily comparable with those of *Tupaia* and chiefly differ in the relatively greater size of the dorsal and ventral elements.

The *anterodorsal nucleus* consists of medium-sized rounded or subangular cells with darkly staining cytoplasm, closely packed together in the usual characteristic manner. The cells are in general somewhat larger than those of the anteroventral nucleus. Rostrally, however, its component cells are smaller and more rounded than elsewhere, and here the limits of the nucleus are not well defined. It first becomes distinct at about section 20, where it forms a fairly thick crescentic cap of cells with a ventral concavity surmounting the circular anteroventral nucleus. It is bounded dorsally by the stria medullaris and medially by the parataenial nucleus, while laterally the cells, which here are more scattered, are related topographically to the superior thalamic radiations. By section 30, the nucleus has increased slightly in size and the component cells are larger and more uniform. Laterally it has now come into contact with the anterior end of the lateral nucleus. Further caudally, it diminishes and, by section 40, forms a small rounded clump of cells. A few sections more posteriorly it disappears, some of its cells apparently being displaced towards the midline where they form a slender and indistinct bed nucleus for a commissure. Anteriorly, the anterodorsal nucleus is related rostrally and laterally to the thick lateral olfacto-habenular tract, many of whose fibres run through the anterior extremity and lateral part of the nucleus as discrete bundles. The smaller size of the constituent cells in these regions seems to be associated with this denser penetration by the fibres passing up to the stria medullaris. More caudally, the nucleus is still penetrated by these fibres, but in smaller bundles. Laterally, it is related to the thalamic radiations, some of whose fibres enter it. The nucleus also appears to be connected with the subjacent anteroventral nucleus by finer bundles of inter-connecting fibres.

The *anteroventral nucleus* consists of cells of the same type as, but rather smaller than, those of the anterodorsal element. They are also more lightly stained and more scattered in their arrangement. Towards the lateral aspect of the group, the cells tend to be smaller and more closely packed, and in some sections show an obscure lamination as the result of the passage through this part of the nucleus by contributions from the superior thalamic radiations. The nucleus first appears rostrally as a circular group of cells fairly close to the midline. In myelin-stained sections it is quite sharply defined with an even contour

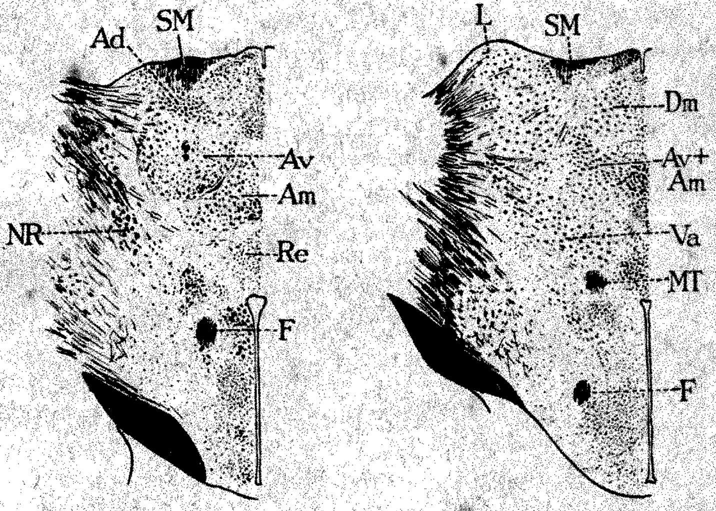


FIG. 3.—Coronal sections (21 and 58) of the thalamus of *Ptilocercus*. (× 10⅔.)

by a capsule of medullated fibres. Here it is bounded laterally by the greater bulk of the lateral olfactohabenular tract, many of whose medial fibres appear to sweep round the nucleus to form a capsule for it. Some of its fibres, however, enter its ventral aspect and pass through it on their way dorsally to the stria medullaris. Between sections 20 and 30, the nucleus reaches its maximum size in transverse section and is of regular circular shape. Here it reaches close to the midline and is penetrated laterally by fibres of the superior thalamic radiations. Dorsolaterally it is in relation with the lateral nucleus of the thalamus and ventromedially with the anteromedial nucleus. By section 40, it has become much diminished in size and appears to have been displaced medioventrally by the enlarging lateral and dorsomedial nuclei. It now loses its individuality, merging with the anteromedial element, while its constituent cells become arranged in rows curving towards the midline and forming evidently a bed nucleus for a commissure which crosses by the massa intermedia of the thalamus.

The *anteromedial nucleus* consists of cells of the same type as those of the ventral element, but as a general rule very slightly larger. It is poorly differentiated and small, being wedged in between the medioventral border of the anteroventral nucleus and the midline. It may be distinguished from the anterior paraventricular nucleus or nucleus dorsalis raphae by the larger size of its cells and by their more scattered disposition. It is connected with its fellow of the opposite side across the midline and caudally it merges with the anteroventral nucleus as described above. Its caudal limit is very difficult to define, but it can no longer be recognized caudal to section 60.

The *mammillothalamic tract* cannot be followed in these preparations to their ultimate termination. It is clear, however, from the direction in which this tract is running that it is mainly associated with the large anteroventral element of the group of anterior nuclei. The relative size of the anteromedial element indicates that if any fibres terminate in it they must be relatively few.

Macroscelides. (Fig. 4.)

The appearance of the anterior nuclei of the thalamus in this aberrant insectivore is very different from those already described, and it would be difficult to homologize the elements except by tracing the connections of the mammillothalamic tract.

The *anterodorsal element* (fig. 5) consists of very large angular and subangular cells with darkly staining cytoplasm. The nucleus is relatively lightly stained and the nucleolus is conspicuous. The cells are closely packed together in a matrix which is throughout permeated with an intricate network of fine medullated fibres and penetrated by bundles of fibres passing dorsally to the stria medullaris. In all sections the nucleus is extremely well defined with an even rounded contour and surrounded by what may be called a "lymph space." Anteriorly it appears in the transverse sections in advance of the other elements of the anterior group of nuclei and immediately caudal to the point where the lateral olfactohabenular tract curves dorsally and backwards to contribute to the stria medullaris. Here it lies close to the dorsal surface of the thalamus, bounded dorsomedially by the large stria medullaris, medially by the nucleus paratænialis, ventrally by the anterior column of the fornix, and laterally by the stria terminalis and its bed nucleus. Traced caudally, the nucleus soon assumes a regular oval form with the long axis directed medioventrally and comes into relation laterally with the anterior extremity of the lateral geniculate body. It reaches its maximum size in transverse section at about section 20. Although its constituent cells maintain their characteristic features, towards the dorsal pole of the nucleus they are found to be rather smaller, more darkly stained and more closely packed together. The nucleus is penetrated freely by bundles of fibres from its lateral and ventral aspects which can be traced laterally into the thalamic radiations and ventrally to the lateral olfactohabenular tract. It seems that most of these bundles of fibres pass through the nucleus to reach the superjacent stria medullaris, and it seems impossible to avoid the conclusion that there is therefore a contribution from the thalamic radiations to the stria medullaris in *Macroscelides*. There is no doubt, also, that some of the fibres entering on the lateral aspect, and therefore derived from the region of the internal capsule, contribute to the intercellular network of the anterodorsal nucleus. Further, these sections would seem to indicate that fibres from the intercellular network of the nucleus emerge and pass into the stria medullaris. However the material may be interpreted, there is a very intimate association between the anterodorsal nucleus and the stria medullaris.

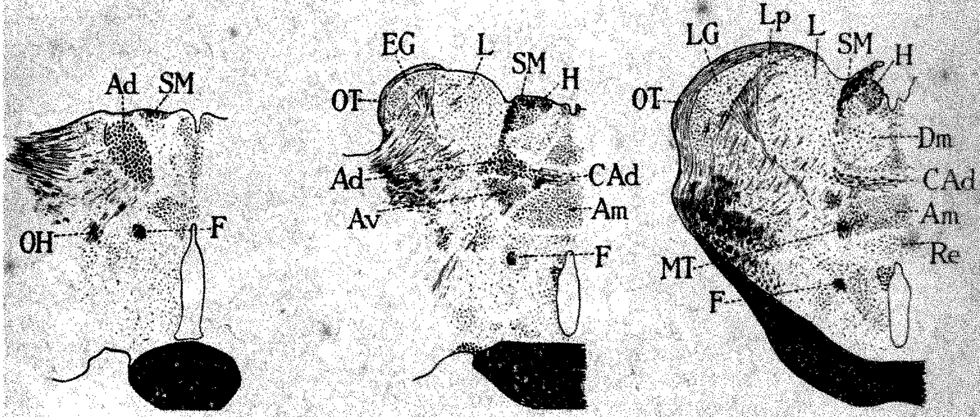


FIG. 4.—Coronal sections (18, 41 and 66) of the thalamus of *Macroscelides*. (× 8.)

By section 25, the nucleus in transverse section has become triangular, being flattened on its lateral aspect by its apposition to the anterior extremity of the lateral thalamic nucleus and ventrally by contact with the anteroventral nucleus. Here, from its medial angle emerge a large number of medullated fibres which cross the midline, forming a commissure which is of conspicuous breadth in the anteroposterior as well as in a dorsoventral direction. The nucleus now appears to be approaching the midline and, by section 30 (with the appearance of the lateral habenular nucleus), it diminishes in size and no longer reaches the dorsal surface of the thalamus. It is still penetrated in its dorsal part by considerable numbers of fibres passing dorsally to the stria medullaris and as it appears to sink below the surface (when traced caudally) it remains for many sections apparently linked up with the stria by bundles of these fibres running dorsally to reach the latter. The nucleus is here related laterally to the anterior end of the lateral nucleus and a fine plexus of medullated fibres extends across the line of junction from one nucleus to the other. Ventrally it is related to the commissura interanterodorsalis which is now better developed, and among the transversely running fibres are strewn the characteristic large angular cells derived from the anterodorsal nucleus and forming a commissural nucleus. By section 45, the anterodorsal nucleus has come to an end but the commissure still persists. While this commissure seems mainly to be composed of fibres that link up the anterodorsal nuclei of the two sides, it also receives fibres from the lateral

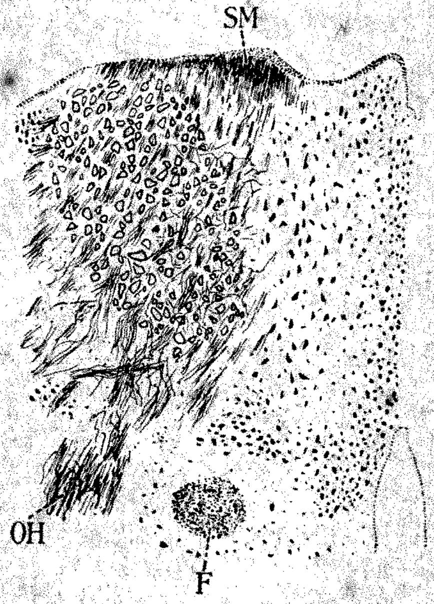


FIG. 5.—Tracing of a coronal section through the anterodorsal nucleus of *Macroscelides*. (× 42⅔.)

thalamic nucleus. Traces of this commissure with its large cells may be found caudally as far as section 70.

The *anteroventral element* of the anterior group of nuclei first appears in this series of transverse sections in section 21 as a group of small granular cells closely packed together and applied to the ventral pole of the anterodorsal nucleus. It is penetrated by discrete bundles of fibres derived from the lateral olfactohabenular tract and, more caudally, by fibres of the thalamic radiations. It takes on a triangular shape, being flattened on its dorsal aspect by apposition with the anterodorsal nucleus in front and to the commissure of this nucleus behind. It is quite sharply separated from the anteromedial element by a cell-free space and is further differentiated from this nucleus by the fact that its constituent cells are smaller, more closely packed, and somewhat more darkly stained. Further, unlike the anteromedial nucleus, it is freely penetrated by contributions from the inferior thalamic radiations. By section 70, the nucleus has disappeared. Throughout its extent, it does not extend further laterally than the lateral limit of the dorsal element and does not reach near the dorsal surface of the thalamus.

The *anteromedial nucleus* consists of larger cells which are angular and somewhat scattered. It appears rostrally in the same transverse plane as the anteroventral nucleus as a small group of cells situated to one side of the median plane. The nuclei of the two sides soon fuse together to form a broad band of cells stretching across the midline ventral to the *commissura interanterodorsalis* and dorsal to the nucleus reuniens. The nucleus is practically free of medullated fibres except caudally where they appear among the cells and pass ventrolaterally in a wavy course to join up with the bundle of Vicq d'Azyr. The nucleus finally disappears at about section 80.

The *mammillothalamic tract* can be followed to its termination particularly well in these sections. Traced dorsally (and anteriorly) the tract reaches the anterior nuclei at the lateral extremity of the anteromedial element towards its caudal limit. At this transverse level, it gives off contributions medially into the anteromedial element and to a lesser extent dorsolaterally into the anteroventral element. These fibres run in among the cells of these nuclei and become lost therein. A little more rostrally, a conspicuous bundle of fibres may be seen running from the tract dorsally into the commissure of the anterodorsal elements. These contributions to the commissure can be followed continuously in a rostral direction until the mammillothalamic tract itself finally reaches the ventral aspect of the commissure (dorsal to the anteromedial and anteroventral nuclei) and disappears as a distinct bundle. The individual fibres passing to the commissure may in many cases be followed some distance. Most of them become lost in the intricate network of the commissure, some can be traced dorsolaterally, clearly aiming for the anterodorsal nucleus of the same side, while many turn medially in the commissure with the evident purpose of crossing the midline to reach the corresponding nucleus of the opposite side. The impression is gained that a large proportion of the fibres of Vicq d'Azyr's bundle thus terminate in connection with the anterodorsal nuclei of the same and opposite sides. A considerable number of fibres also terminate in the anteromedial nucleus, while relatively few reach the anteroventral element.

Erinaceus. (Figs. 5 and 6.)

Sections of the thalamus of this primitive insectivore give the impression that the cells of the thalamic nuclei are much more loosely packed than is the case with the other insectivora examined. As a consequence, the nuclei are more diffuse and not so clearly circumscribed. It is partly because of this fact that the identification of the elements of the anterior group of nuclei offers considerable difficulty. Indeed, without the study of the thalamus of *Macroscelides* as a link, it would hardly be possible by ordinary methods to make a certain comparison with the nuclei of the tree-shews.

The *anterodorsal nucleus* presents the greatest difficulty for identification. There is no circumscribed group of cells comparable with that found in the other forms, especially as it appears in *Macroscelides*. It may be said at once that if this element is represented in the hedgehog, it is extremely poorly defined and of insignificant size.

In the transverse series of sections there appears rostrally among the olfactohabenular fibres as they are approaching the dorsal surface of the thalamus a few scattered cells of angular and sub-angular shape, larger than the cells in most parts of the thalamus (with the exception of those forming the dorsomedial nucleus), and with cytoplasm staining rather more deeply than is the case with the cells of neighbouring nuclei. They lie in a matrix which stains a little darker with methylene blue than surrounding areas and which in iron-hæmotoxylin sections is seen to be richly permeated with fine medullated fibres. The cells form a loosely packed group of oval form with its long axis directed vertically.

It lies medial to the main mass of fibres of the lateral olfactohabenular tract and dorsolateral to the anterior end of the nucleus reuniens. The group reaches a size shown in fig. 5a and then rapidly diminishes caudally. Its caudal extremity in transverse sections cannot be defined for it seems to be connected by a scattered band of cells with the anterior extremity of the dorsomedial nucleus of the thalamus. In sagittal sections, this group can be identified (fig. 6) lying anterodorsally to the small-celled anteroventral nucleus, in among the fibres which are passing up to form the stria medullaris. In these sections also it can be seen to be linked up with the anterior extremity of the dorsomedial nucleus by scattered and smaller cells. In the absence of any alternative interpretation, this group of cells may be provisionally regarded as representing the anterodorsal nucleus in *Erinaceus* because of the following characters: (1) Position. It may be pointed out, in this connection, that the cells lie in a relatively more anteroventral position than the anterodorsal nucleus of the other forms, and, moreover, in a position where Cajal's nucleus of the stria medullaris might be expected to lie. But the cells of the latter nucleus are typically very small and the position of the other anterior nuclear elements in *Erinaceus* differs from the condition in the other insectivora. (2) Relative size and staining properties of cells. (3) The group is permeated by fibres of the lateral olfactohabenular tract. (4) The cells lie in a matrix of fine

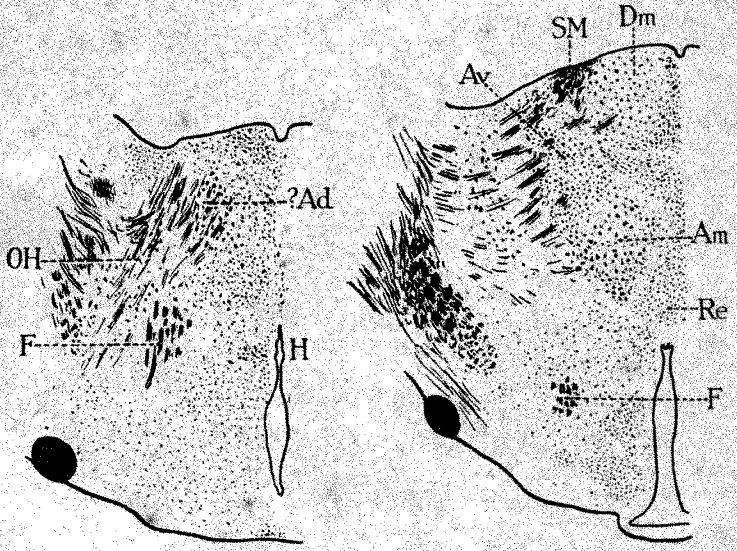


FIG. 6.—Coronal sections (5 and 16) of the thalamus of *Erinaceus*. (× 10⅔.)

interlacing medullated fibres. In these features, this group of cells resembles the anterodorsal nucleus in other mammals. In any case, however, the small size and poorly defined nature of this group of cells should be emphasized. No interanterodorsal commissure could be recognized.

The *anteroventral nucleus*, although of irregular shape, can be identified by the small size of its constituent cells. Its general disposition corresponds to the same element in *Macroscelides* though it is much larger in extent. Immediately caudal to the plane at which the group labelled the anterodorsal nucleus ceases to be recognizable as a definite entity there appears a group of small triangular and rounded cells which are relatively closely packed together. It is related dorsally to the anterior end of the dorsomedial nucleus, laterally to the reticular nucleus and internal capsule, and medioventrally to the anteromedial nucleus and the nucleus reuniens. In its most rostral plane this small-celled group, the anteroventral nucleus, is irregularly circular in transverse section, but it rapidly assumes a triangular shape with its apex directed dorsolaterally towards the dorsal surface of the thalamus and its base ventromedially where it abuts against the anteromedial element. It is penetrated by compact bundles of fibres from the thalamic radiations which give to it a coarsely reticulated appearance in methylene blue sections. In its maximum extent, the nucleus extends dorsally between the nucleus reticulatus and the nucleus dorsomedialis

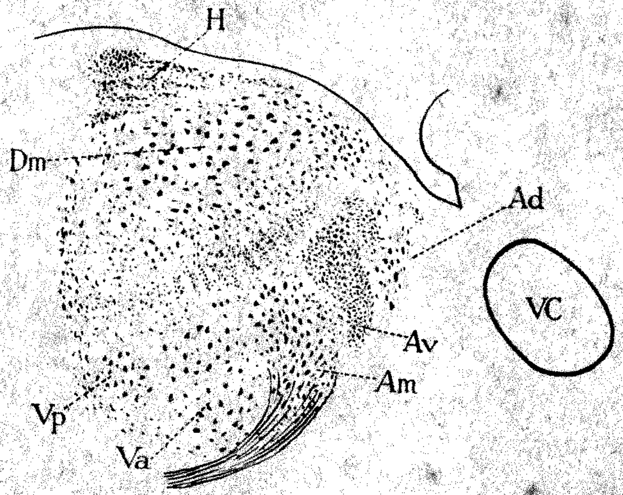


FIG. 7.—Sagittal section of the dorsal part of the thalamus of *Erinaceus*, close to the midline. The position of the mammillothalamic tract has been superimposed from the adjacent section stained with iron-hæmotoxylin. (× 16.)

to reach the dorsal surface of the thalamus. More caudally, it recedes from the dorsal surface, being replaced by the anterior end of the lateral thalamic nucleus, and then gradually diminishes in size as it is traced backwards until it disappears. In sagittal sections, this nucleus is also clearly defined, lying anterodorsally to the anteromedial element, its more dorsal part being penetrated by fibres of the olfactohabenular tract.

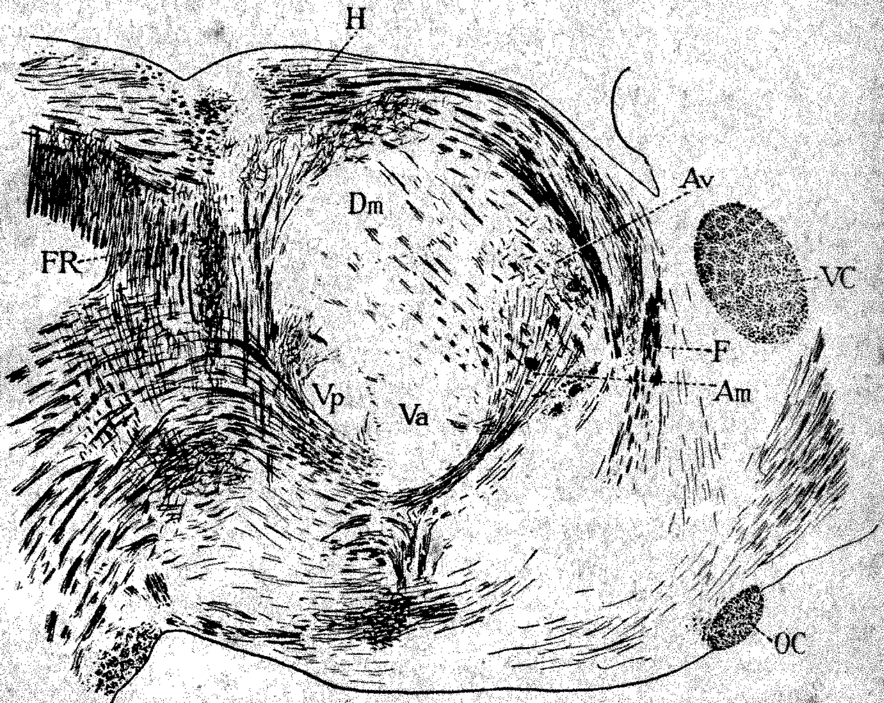


Fig. 8.—Sagittal section of the thalamus of *Erinaceus*, showing the fibre tracts. (× 16.)

The *anteromedial nucleus* makes its appearance at about the same transverse level as the anteroventral element. Its cells are larger than those of the latter, more scattered in their arrangement, and triangular or polygonal in shape. Rostrally it forms an oblique band of cells interposed between the anteroventral nucleus and the nucleus reuniens, and directed dorsomedially towards the median raphe where it appears to be linked up with the nucleus of the opposite side by similar cells extending across the midline. The caudal extremity of this nucleus is extremely difficult to define in transverse sections, for it seems to pass insensibly into the ventral nuclei of the thalamus. In sagittal sections, however, the distinction is clearer. Here the cells of the anteromedial nucleus tend to be arranged in irregular rows and to lie with their long axes parallel to the brush-like termination of the fibres of the mammillothalamic tract. It is seen also that the cells are more closely packed together, and are a little smaller in general than those of the ventral nuclei. Moreover, in iron-hæmotoxylin sections, the nucleus is clearly defined by the fibres of the mammillothalamic tract.

The *mammillothalamic tract* (fig. 8), compared for instance with *Tupaia*, is much shorter and runs a more oblique course. At its upper extremity, it breaks up into a brush of fine fibres which run throughout the anteromedial nucleus. Many of these fine fibres can be traced to the dorsal aspect of the nucleus and it is certain that they pass on to make connection with the anteroventral element, even though such fibres could not be traced individually in continuity as far as this.

DISCUSSION.

It has been shown that three elements of the anterior group of nuclei can usually be recognized in the thalamus, but that these elements, even within the limits of the insectivora, show a great degree of variation in their relative size and differentiation, and in the characters of their constituent cells. It would be hardly possible, for instance, to make a comparison between the anterior nuclei of *Tupaia* and *Erinaceus* without noting their relation to the terminal fibres of the mammillothalamic tract and without the study of the thalamus of *Macroscelides* as in some way an intermediate link.

In the tree-shrews, the appearance of the anterior nuclei resembles that found in most mammals of a more specialized or advanced type. In *Macroscelides* an unusual condition is found which parallels the unusual features found in the brain of this animal generally. In *Erinaceus*, the interpretation, at first sight, is not easy. Judging from figures of the thalamus of the opossum given by Tsai [21], the anterior nuclei in this primitive animal closely resembles the condition found in the hedgehog. Moreover, the anterior nuclei of the hedgehog bear a much closer resemblance to the nuclear groups of the reptilian thalamus which have been regarded as equivalent to the anterior nuclei of mammals than is the case with the other insectivores. This is in accord with the general primitive features of the brain of *Erinaceus*.

It will be convenient to discuss separately the three anterior nuclei. The anterodorsal nucleus lies close to the dorsal surface of the thalamus in among the fibres of the olfactohabenular tract streaming up to contribute to the stria medullaris. The constituent cells lie in a meshwork of fine medullated fibres, and are characterized by their deeply staining cytoplasm and their closely packed arrangement. When the nucleus is well developed, the cells are conspicuous for their large size. As regards the fibre connections of the anterodorsal nucleus, Cajal [4] found in his rodent material that fibres of the mammillothalamic tract reach it after having penetrated the anteroventral nucleus. This observation does not seem to have been corroborated by other authorities who have paid attention to this point. Thus Gurdjian, in his studies on the thalamus of the albino rat, could find no direct connection between the anterodorsal nucleus and the bundle of Vicq d'Azyr. In *Macroscelides,* however, where this nucleus is very conspicuously developed, the connection is obvious enough and such cases lead one to suppose that in those animals where the nucleus is relatively smaller the connection is also present although it may not be detected by ordinary histological methods. Laterally the anterodorsal nucleus is in intimate relation with the superior thalamic radiations, but the significance of these fibre connections of the anterior nuclei will be discussed below with the anteroventral nucleus. Kappers [12] believes that they are partly striatal and partly cortical in their termination, and that the thalamo-cortical fibres of the anterior group of nuclei probably arise from the dorsal element (Monakow's n. anterior C). He quotes Rutishauser's [18] observation that this element is found much degenerated after experimental lesions of the frontal region of the cerebral cortex. The close and constant relation which the anterodorsal nucleus always bears to the stria medullaris suggests the possibility of a functional relation. The sections of *Macroscelides* brain, indeed, do seem to indicate a direct fibre connection between the intercellular network of fibres in the anterodorsal nucleus and the stria medullaris, though a decisive statement cannot be made upon this point. Kappers observes that this nucleus lies apparently interpolated in the course of the tænia and that it seems to belong to this fibre tract. Papez [17] states definitely that in the cat his dorsomedial nucleus (= n. anterodorsalis) receives fibres from the olfactohabenular tract. On the other hand, Cajal emphatically remarks that while the nucleus (his angular nucleus) is traversed by fibres passing to the stria medullaris, these fibres all pass through it without interruption. This is clearly a matter which requires further investigation.

It has been shown that the anterodorsal nucleus attains a remarkable development in *Macroscelides.* In this, it parallels and surpasses the condition which seems to be especially characteristic of the rodents as a group. In this connection it is relevant to note that the brain of *Macroscelides* shows many other resemblances to that of rodents, and especially in the strong development of the subsplenial portion of the hippocampus and the relatively great extent of the retrosplenial and associated cortical areas. In discussing the termination of the thalamo-cortical fibres which he believes are connected with the anterior nuclei, Kappers states that it is not certainly decided whether these pass to the frontal lobes or to the regio cingularis or retrosplenialis of the cortex. The latter suggestion would seem to derive some support from the condition in the brains of rodents and especially *Macroscelides*, where an inordinate development of the anterodorsal nucleus is associated with an unusual development of the retrosplenial and cingular areas of the cortex cerebri [1, 7]. That the development of this nucleus is not

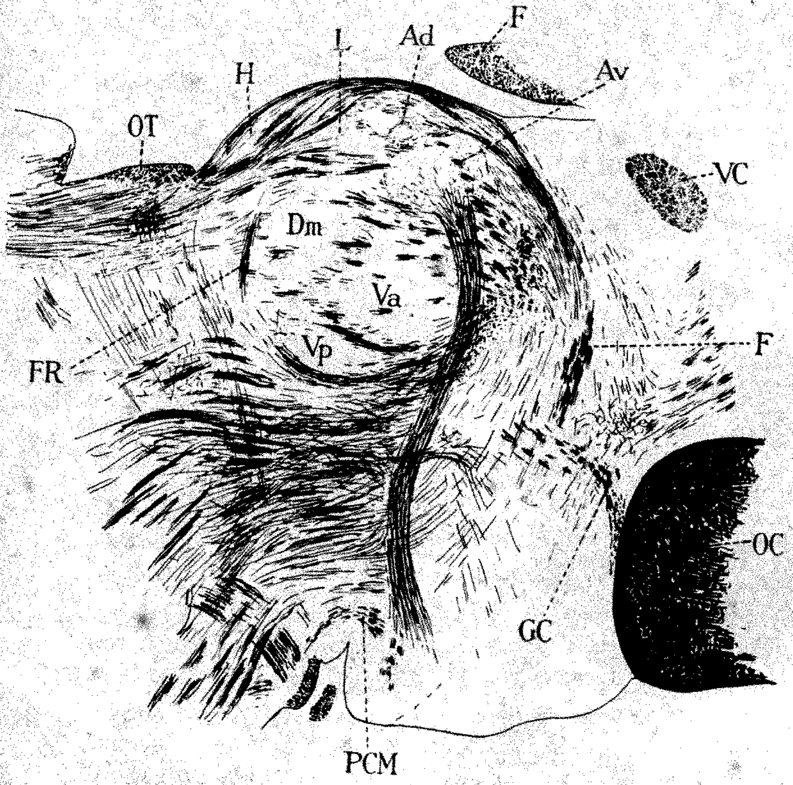


FIG. 9.—Sagittal section of the thalamus of *Tupaia minor*, showing the fibre tracts. The position of the lower end of the mammillothalamic tract has been traced in from an adjacent section in order to show the whole course of this tract. (× 16.)

directly related to the primary and secondary olfactory centres is indicated by the fact that in *Erinaceus* it does not exist, at least as a clearly-defined group of cells. Such an example also indicates that a well-developed anterodorsal nucleus is not to be regarded as a primitive mammalian characteristic as has been done by some authors. Furthermore, the condition in the very primitive brain of *Erinaceus*, together with the absence of any element in the reptilian thalamus which can be directly compared with the anterodorsal nucleus, leads to the conclusion that the development of this nucleus is a mammalian character which becomes specialized in certain mammalian groups such as the rodents and the Macroscelididæ.

In *Ptilocercus*, the anterodorsal nucleus is, in relation to the anteroventral nucleus, much smaller than in *Macroscelides*, and its constituent cells are not nearly so large. In *Tupaia*, the nucleus is distinctly smaller than in *Ptilocercus*, and its cells are not in general larger than those of the other anterior nuclei. In this insectivore a condition has been reached which, indeed, approaches that characteristic of the Primates. In the latter group, the nucleus, if traced through different representatives from the lowest to the highest, shows a progressive tendency towards shrinkage and disappearance. These comparative observations have led to fallacious conclusions regarding the relation of the development of the nucleus to that of the olfactory regions of the brain. It may be noted, in this regard, that in *Tarsius*, in which the olfactory bulb and associated centres show a marked reduction, the anterodorsal nucleus is quite conspicuous.

The anteroventral nucleus is the element which forms such a conspicuous spherical and well-defined nucleus in the brains of most mammals, and which is often referred to as the anterior nucleus, the nucleus dorsalis, or the nucleus dorsalis magnus. It is commonly regarded as the main site of termination of the bundle of Vicq d'Azyr, but this is by no means necessarily so. The proportion of the fibres of the mammillothalamic tract which end in this nucleus depends upon the size of the nucleus relative to the other anterior nuclei. Thus, for instance, in the rat in which the anteromedial nucleus is relatively well developed, Gurdjian found that most of the fibres terminated in the latter nucleus and only a comparatively small proportion in the anteroventral nucleus. In *Macroscelides*, again, where the anterodorsal nucleus is so large, the majority of the fibres of the mammillothalamic tract end here. Abundant efferent fibres pass out from the lateral aspect of the anteroventral nucleus into the superior thalamic radiations. The ques-

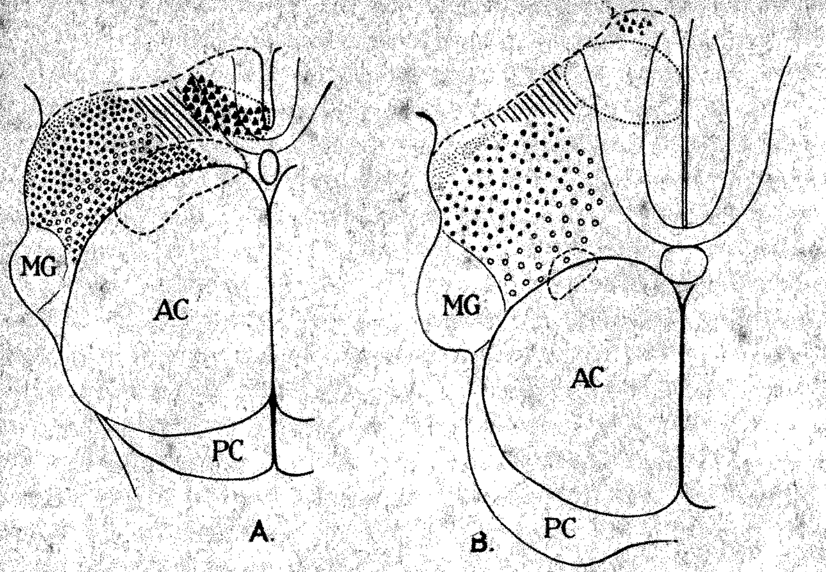


FIG. 10.—Dorsal view of the thalamus of (*a*) *Macroscelides* and (*b*) *Erinaceus* reconstructed from the coronal sections. In this and the next figure, some of the thalamic nuclei have been projected on to the dorsal surface of the thalamus. (× 8.) Black triangles = anterodorsal nucleus. Dotted line = anteroventral and anteromedial nuclei. Oblique lines = anterior part of the lateral nucleus. Fine dots = ventral nucleus of lateral geniculate body. Coarse dots = dorsal nucleus of lateral geniculate body. Circles = pars posterior of lateral nucleus. Crosses = pretectal nucleus. Interrupted line = posterior nucleus.

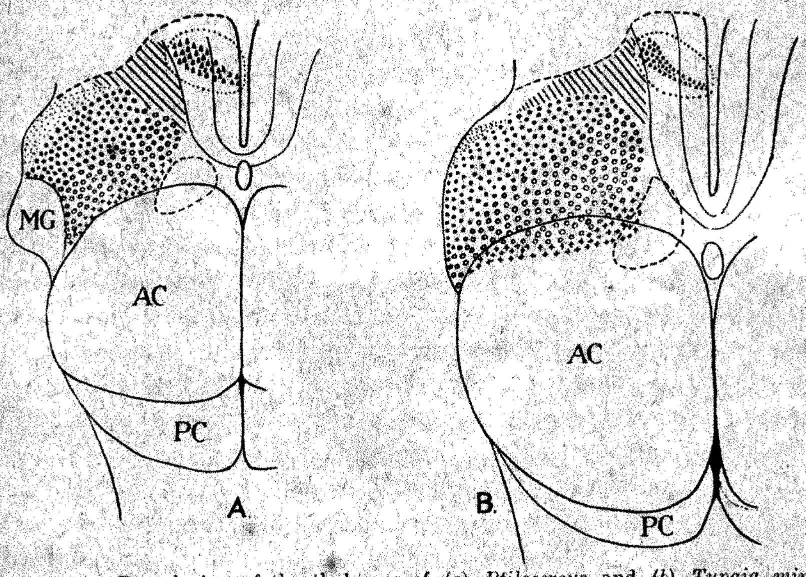


FIG. 11.—Dorsal view of the thalamus of (*a*) *Ptilocercus* and (*b*) *Tupaia minor*, reconstructed from the coronal sections. Nuclei indicated as in the previous figure. (× 8.)

tion as to whether these fibres terminate in the cortex or whether they only reach the striatum raises the interesting problem of a possible cortical connection of the anterior nucleus as a whole. As long ago as 1895, Monakow [15] adduced experimental and clinical evidence to suggest such a connection with the upper frontal convolutions or with the suprasplenial portion of the gyrus fornicatus. Lindon Mellus [14] found degenerated fibres passing to the anterior nucleus of the thalamus after experimental lesions in the frontal lobe of the monkey's brain. Similar findings by Rütishauser have been referred to above. Livini described fibres connecting the anterior nucleus with the gyrus fornicatus in *Hypsiprimnus*, and Sachs [19] accepts the possibility of such a connection in his comparative study of the mammalian thalamus. In another publication [20] dealing with an experimental study of the thalamus, however, the latter author denies the existence of any fibres passing direct from the anterior nucleus to the cortex, and states that these fibres terminate in the striatum. It should be noted that Sachs refers only to the anteroventral nucleus (his n. dorsalis magnus) and in this particular reference does not include a discussion of the anterodorsal element (his n. disseminatus). Cajal states definitely that the efferent fibres of his dorsal nucleus penetrate the corpus striatum and thus constitute an important thalamo-cortical fibre system. Kappers [12] sums up the evidence by expressing his belief that the anterior nucleus does give off cortical projection fibres. He deems it probable that these cortical fibres arise in the anterodorsal nucleus, while the main nucleus, the anteroventral nucleus, gives off most of the striatal fibres. In harmony with this idea is the fact that, as pointed out above, there appears to be no representative of the anterodorsal element in the reptilian brain in which a neopallium is hardly developed except possibly as a very primordial and elementary structure.

In *Erinaceus* and *Macroscelides*, the anteroventral nucleus has not the characteristic circular form, nor is it clearly defined by a capsule of medullated fibres as it is in most mammalian brains. It is rather of an irregular triangular shape extending dorsolaterally and, in the case of *Erinaceus*, reaching to the dorsal surface of the thalamus. It is relatively small in *Macroscelides*, but occupies a large area of the frontal part of the thalamus in *Erinaceus*. In the latter insectivore, the nucleus has a striking general appearance to the nucleus dorsolateralis anterior of the reptilian thalamus described by Huber and Crossby [11], and by Cairney [3]. This nucleus forms the lateral part of the cell-group in the reptilian thalamus described by De Lange [13] and Kappers as the anterior nucleus. According to De Lange, there is in *Draco volans* a definite mammillothalamic tract terminating in this nucleus. Plentiful striothalamic connections between the nucleus dorsolateralis anterior of reptiles and the striatal regions of the forebrain by the lateral forebrain bundle have been described by various authors. Huber and Crossby conclude that one may regard the nucleus as the anlage of the portion of the nucleus anterior of mammals which has connections with the frontal cortical areas, or the somatic part of the anterior nucleus. A comparison with the thalamus of *Erinaceus* would appear to indicate that the n. dorsolateralis anterior is equivalent to the anteroventral nucleus of mammals, the thalamostriatal connections of which are certain, while, as is suggested above, it is the anterodorsal nucleus which is related to the cortex.

In the *Tupaiidæ*, the anteroventral nucleus is of a well-defined spherical form as in the brains of the higher mammals generally. It is somewhat smaller relatively in *Tupaia minor* than in *Ptilocercus*. This difference might be associated with the relative development of the olfactory centres of the brain in the two animals, but a survey of the brains of a large number of mammals shows no direct relation between the size of the anteroventral nucleus and the olfactory centres. In Primates, for instance, and even in Man, the anteroventral nucleus is well developed and remarkably differentiated, although the primary and secondary olfactory centres are much reduced.

The anteromedial nucleus is the least well defined of the anterior nuclei, and by many authors it has been dissociated from the anterior group of nuclei and included in the medial group. But its relation to the terminals of the mammillothalamic tract indicate its true position among the thalamic nuclei. It has already been pointed out that Gurdjian found most of the fibres of this tract terminating in this nucleus in the rat. In *Erinaceus*, the same condition is found, the termination of the tract being much more closely related to the anteromedial than to the anteroventral nucleus. It is doubtful whether this element is related to the fibres of the thalamic radiations as are the other elements of the anterior nucleus. Gurdjian states that the anteromedial nucleus in the rat receives "but very few fibres (if any at all) from this system." Our observations on the same nucleus in the insectivora point to the same conclusion. It is probable, indeed, that this nucleus belongs to the palæothalamus and is only in direct fibre connection with other thalamic nuclei and with the hypothalamus. A comparison with the primitive condition in the thalamus of *Erinaceus* suggests strongly that the reptilian nucleus dorsomedialis anterior, (cf. Huber and Crossby, and Cairney) is its homologue. It is this nucleus which appears to be in most direct relation with the mammillothalamic tract described by De Lange in reptiles. According to Cairney, also, in Sphenodon, it receives part of his fasciculus diencephalicus periventricularis which he intimates is the equivalent of De Lange's mammillothalamic tract. Moreover, the dorsomedial anterior nucleus of reptiles in contrast to the dorsolateral anterior nucleus is not connected to the striatum by thalamostriatal fibres, or only to a very insignificant extent.

While in most mammalian brains the cellular elements of the anteromedial nucleus do not differ to any marked extent from those of the anteroventral nucleus, in *Erinaceus*, and to a lesser extent in *Macroscelides*, the cell types are clearly distinct. In these insectivores, also, the anteromedial nucleus is large and well differentiated in comparison with the anteroventral nucleus. This is a feature to be anticipated in the most primitive mammalian brains in which the palæothalamic nuclei may be expected to be relatively more obtrusive. In higher forms, the nucleus is more diffuse and in no way clearly delimited in sections stained to display the cyto-architecture of the thalamus. It also undergoes a reduction in size in relation to the anteroventral element. We may say, then, that the comparative anatomical evidence favours the following interpretation of the significance of the anterior thalamic nuclei. These nuclei serve for the reception of impulses relayed on from the mammillary bodies. This part of the hypothalamus is primitively connected with the mid-brain and hind-brain by way of the mammillotegmental fibres, as well as with the archipallium by the fornix. In some reptiles there is evidence of a mammillothalamic tract which ascends to the anterior and dorsal part of the thalamus. This tract at first mainly terminates in the anteromedial nucleus (or its homologue) in reptiles and primitive mammals, and the anteromedial nucleus is to be regarded as a part of the palæothalamus and not primarily a somatic centre. The somatic part of the anterior group of nuclei is first represented by the anteroventral nucleus (or its reptilian equivalent) which relays on to the neostriatum. Finally a third element, the anterodorsal nucleus, which is not definitely recognizable in reptiles and the most primitive mammals, possibly serves as a relay station through which impulses derived from the mammillary region may be carried on to the cerebral cortex. This third element only reaches a marked development in certain specialized mammalian brains, such as the brains of the Macroscelididæ and (to a lesser extent) the rodents.

REFERENCES.

[1] Brodmann, K. "Vergleichende Lokalisationslehre der Grosshirnrinde," Leipzig, 1909.

[2] Brunner, and Spiegel, E. A. "Vergleichende anatomische Studien am Hapalidengehirn," *Folia Neurobiologica*, 1918, **11**, 171.

[3] Cairney, J. "The Forebrain of Sphenodon Punctatum," *Journ. of Comp. Neur.*, 1926-27, **42**, 256.

[4] Cajal, S. R. y. "Histologie du Système Nerveux," 1911.

[5] Clark, W. E. Le Gros. "The Brain of Tupaia Minor," *Proc. Zool. Soc. London*, 1925, 1185.

[6] *Idem.* "The Anatomy of Ptilocercus Lowii," *Ibid*, 1926, 1179.

[7] *Idem.* "The Brain of the Macroscelididæ," *Journ. of Anat.*, 1928, **62**, 245.

[8] *Idem.* "The Thalamus of Tupaia Minor," *Ibid.*, 1929, **63**, 177.

[9] Fortuyn, B. D. "Die Ontogenie der Kerne des Zwischenhirns beim Kaninchen," *Arch. f. Anat. und Phys.*, 1912, 303.

[10] Gurdjian, E. S. "The Diencephalon of the Albino Rat," *Journ. of Comp. Neur.*, 1927, **43**, 1.

[11] Huber, G. C., and Crosby, E. "On Thalamic and Tectal Nuclei in the Brain of the American Alligator," *Ibid.*, 1926, **40**, 97.

[12] Kappers, C. U. Ariens. "Die vergleichende Anatomie des Nervensystems der Wirbelthiere und des Menschen," Haarlem, 1921.

[13] de Lange, S. J. "Das Zwischenhirn und das Mittelhirn der Reptilien," *Folia Neurobiologica*, 1918, **7**, 67.

[14] Lindon Mellus. "Relations of the Frontal Lobe in the Monkey," *Amer. Journ. of Anat.*, 1907-8, **7**, 227.

[15] Monakow, von. "Experimentelle und pathologisch-anatomische Untersuchungen über die Haubenregion, etc.," *Arch f. Psych.*, 1895, **27**, 1.

[16] Malone, E. F. "Ueber die Kerne des menschlichen Diencephalon," *Abh. der Kgl. Preuss. Akad. d. Wissen*, 1910, 1.

[17] Papez, J. W. "Comparative Neurology," New York, 1929.

[18] Rütishauser. "Experimentelle Beitrag zur Stabkranzfaserung im Frontalhirn," *Monatsch. f. Psych. u. Neur.*, 1889, **5**.

[19] Sachs, E. "Eine vergleichendanatomische Studie des Thalamus Opticus der Saugethiere," *Arb. aus dem. Neur. Inst Wiener Univ*, 1909, **17**, 280.

[20] *Idem.* "On the Structure and Functional Relations of the Optic Thalamus," *Brain*, 1909, **32**, 95.

[21] Tsai, C. "The Optic Tracts and Centres in the Opossum," *Journ. of Comp. Neur.*, 1925, **39**, 173.

[22] Winkler and Potter. "An Anatomical Guide to the Experimental Researches on the Rabbit's Brain," Versluys, Amsterdam, 1911.

[23] Woollard, H. H. "Epicritic and Dyscritic Systems in a Primitive Primate," *Journ. of Anat.*, 1928, **72**, 276.

THE SIGNIFICANCE OF SOME VARIATIONS IN THE KNEE-JERK IN DISEASES OF THE CENTRAL NERVOUS SYSTEM.[1]

BY E. A. BLAKE PRITCHARD, M.D., M.R.C.P.

Assistant in the Medical Unit, University College Hospital, and Registrar to the Hospital for Epilepsy and Paralysis, Maida Vale.

CONTENTS.

I.—THE PURPOSE AND SCOPE OF THE WORK HERE REPORTED.

PAGE
Introduction 360

The Clinical Significance of the Knee-jerk.

Its Occurrence 362
Variations in Form 363
The Purpose of the Present Work 364

The Conditions to be satisfied.

The Excitability of the Muscle 364
The Essential Nature of the Stimulus 366
The Essential Nature of the Response 370
The Necessary Anatomical Conditions 371
Accessory Factors to be controlled or stabilized 372
The Time Intervals to be measured 375

II.—THE METHOD AND APPARATUS USED.

Description of the Apparatus 377
The Records obtained 379

III.—THE RESULTS OBTAINED.

Facilitation and inhibition 380
The Influence of the Tension Background and of the Stimulus 380
The Latent Period 384

The Muscle Response analysed:

The Contraction Phase 384
The Plateau 387
The Relaxation Phase 389
Clonus 391

The Characteristics of Responses under Different Clinical Conditions

The Spastic Knee-jerk 394
The Hypotonic Knee-jerk 395
The Choreic Knee-jerk 396
The Parkinsonian Knee-jerk 397

---

[1] From the Department of Neurology, University College Hospital, and the National Hospital, Queen Square. The expenses of this investigation were met by Grants from the Medical Research Council, and the Board of Management of the National Hospital.

PAGE
IV.—SUMMARY 397
V.—APPENDIX I The Knee-jerk as a Myotatic Reflex 399
II. The Latent Period 406
III. Comparison with other Muscle Responses 408
IV. A Discussion of the Available Methods 409
V. The Methods adopted for measuring the Curves 413
VI.—EXAMPLES OF THE RESPONSES RECORDED. Figs. 5 to 29 417
VII.—TABLES OBTAINED BY MEASUREMENT OF THE CURVES. Tables I to IV .. 419
VIII.—BIBLIOGRAPHICAL REFERENCES 421

INTRODUCTION.

DURING the course of the year 1875 there appeared in the *Archives für Psychiatrie und Nervenkrankungen* two articles, one by Erb and the other by Westphal, both dealing with the knee-jerk. These appear to have been the first recorded studies of a phenomenon to which references can be traced in medical literature as far back as the last quarter of the eighteenth century and which had received current recognition in Charcot's clinic since 1862.

It is of interest to note that from their first approach to this subject these two observers differed upon one vital point in the interpretation of what occurred, and this was reflected in the title given by each to his paper—Erb describing the "Sehnenreflexe," and Westphal, with less avowed decision, "eine Bewegungserscheinung." This difference in interpretation persists to the present day, even after very many contributions have been made towards its settlement. Erb held that the knee-jerk and allied reflexes were true "reflexes" involving nervous paths; Westphal said that they were local muscle responses dependent upon peripheral excitability alone to which central nervous connections were purely adventitious.

The work devoted to the study of these reflexes and the articles written about them are difficult of enumeration. In 1893, only eighteen years later, Sternberg in his monograph quoted from over 300 articles written around the subject and from the published results of thirty-five different workers who had recorded graphically movements of the limbs elicited as tendon reflexes. Since that time, although the methods of recording and the clinical observations have multiplied very greatly, the important questions with which discussion has been concerned are few and they may be briefly summarized thus:—

(1) The occurrence of the knee-jerk and the conditions associated with its absence or exaggeration.

(2) The qualitative changes of form of this response found in persons

suffering from various diseases and the means of reproducing these changes experimentally.

(3) The nature of the phenomenon—a response to local muscle irritability or to a nervous reflex.

The observations and experiments upon which this paper is based have some bearing upon each of these questions, and the results of the method here introduced of recording muscular contractions are offered as a contribution to the subject as a whole.

THE CLINICAL SIGNIFICANCE OF THE KNEE-JERK.

The prominent place which examination of the tendon response has held in the routine of neurological investigation is mainly due to the fact that the percussion hammer provides the clinician with a form of interrogation which forces from the nervous system a succinct answer, as Babinski [2] has phrased it. This answer is in the form of a clearly visible somatic change—a piece of objective evidence which if properly interpreted can throw light upon the integrity or impairment of definite and distinct parts of the nervous system. For its interpretation to be sound it must be systematized and correlated with the other relevant clinical and pathological evidence. Changes in this particular reflex associated with various conditions and lesions have been recorded as simple presence or absence of the reflex, its diminution or exaggeration and certain characteristic changes in form.

The attempt to explain these clinical observations in terms of physiological function is not confined to recent years, but it is only recently that physiology has been able to offer any acceptable explanation. Function in the physiological sense is inseparably bound up with the idea of purpose, but for the tendon reflexes no clearly satisfactory purpose can be claimed. Of earlier writers, Erb [18], de Watteville [92] and Mommsen [56] pronounced them to be purposeless with all the more alacrity because this accorded with their view that they were local, peripheral phenomena. Sternberg concluded that they were developed to provide a protection to the joints against sudden shock by acting as splints both to aid the ligament in keeping the joint surfaces in apposition and to prevent any extreme displacement of the limb segments; their exaggeration with the development of spasticity when the limb was completely paralysed for voluntary efforts, and the arthropathies which often resulted when they were lost as in tabes dorsalis, being adduced in confirmation of this view. Even if regarded in the light of recent work as particular examples of the stretch reflex, the postural functions of which are readily acceptable, their mechanism is explained but still not their purpose. This view does, however, provide an explanation for certain clinical correlates of the tendon-jerks, muscle tone, clonus, &c., and helps to systematize many associated but otherwise unrelated clinical observations. These observations, which we have seen above to be concerned with certain changes in the reflexes, may now be considered in detail.

THE PRESENCE OR ABSENCE OF THE KNEE-JERK.

In common with the other tendon reflexes the knee-jerks are notoriously difficult to elicit in infants, but their presence is so nearly universal in adults who in other respects at least show no signs of abnormality, that they are usually regarded as constantly present. Of the clinicians who have recorded their failures to elicit the knee-jerk in such subjects the following list provides typical examples:—

Pelizaeus [63], in 2,403 children, 0 failures.

Sternberg [83], in 6,000 adults, 1 failure (in whom all tendon reflexes were lost).

Jendrassik [44], in 1,000 adults, 1 failure (a case of diabetes).

Zenner [96], in 1,000 adults, 2 failures.

Block [8] reports 0·72 per cent. failures.

Berger [7] reports 1·56 per cent. failures.

Eulenberg [19] reports 4·8 per cent. failures.

When it is remembered that certain conditions such as even a slight peripheral neuritis may abolish the tendon responses long after other signs have disappeared, much value cannot be attached to their loss as an isolated abnormality, and to state, as Hoffmann [36] has stated, that if "in normal patients" no tendon reflex can be elicited with the help of the usual facilitation manœuvres then "this is pathological," is meaningless.

The cases in which the absence of the knee-jerk is of known significance fall into two main groups—those in which it has shared a fate common to all the tendon reflexes of that person, and those in which its absence contrasts with the preservation of the other knee-jerk or of neighbouring reflexes such as the ankle-jerk. Examples of the former group are seen in the conditions of marasmus, weakness and encephalitis (Sternberg [83]), profound asphyxia and narcosis (Risien Russell [70]) and after epileptic fits (Beevor [6]), conditions all of general nervous inexcitability or exhaustion. Their absence, with preservation of the ankle-jerks, is of much more definite and localizing significance.

Westphal [95] himself pointed out that this occurred in cases of spinal lesion. Sternberg [83] quotes cases showing that this usually argues a local nuclear lesion involving the origin of the anterior roots of nerves which go to the quadriceps femoris; but he amplifies Westphal's observation that it may occur after some fevers, typhus, smallpox, &c., by adding to this list the terminal stages of many infective diseases and the recovery phase from an epileptic fit. The particular value of such loss when it is restricted to one knee-jerk lies in the evidence it gives for localizing the lesion in some part of the essential nervous connection of the muscle which fails to respond.

QUALITATIVE CHANGES IN THE KNEE-JERKS.

Impairment of the knee-jerks has been recorded in muscular diseases affecting the quadriceps femoris, and in peripheral neuritis, tumours, &c., interrupting either its sensory or its motor connections.

Within the central nervous system the lesions which give impairment or exaggeration of the knee-jerks have gradually been localized in definite tracts or centres whose involvement may be expected to give characteristic changes in one or other of these directions. Thus a lesion of the pyramidal tracts in any part of their paths from the cortex to the lumbar cord leads eventually to exaggeration of the reflexes, whatever may be the much discussed mechanism providing this effect. Lesions of the cerebellum have frequently been claimed to provide an impairment of the knee-jerks, an unilateral lesion exercising this effect over the ipsilateral reflex (Jackson [40], Bastian [4], Bowlby [12], Fergusson [21], &c.), but it is doubtful if this is strictly true, as lesions rigidly limited to the cerebellum have frequently failed to show this effect.

That exaggeration of the knee-jerks may be seen in neurotic and highly excitable subjects in the absence of organic lesions has always been recognized, and many attempts have been made to discriminate between the exaggerations due to this condition and those due to organic lesions. Lewandowsky [46] held that the addition of an adductor contraction to that in the quadriceps was definite evidence of organic disease, and Hoffmann [36] that maintained clonus was similarly conclusive. It is, however, generally recognised that neither of these provides an absolute criterion for the decision in question and no other is as yet forthcoming.

Apart from exaggeration and diminution, changes in form of the contraction have been described only in chorea and cerebellar disease—

the "sustained" jerk of the one and the "pendular" jerk of the other being well recognized.

PURPOSE OF THE PRESENT WORK.

The above clinical variations have been recognized as detectable in the knee-jerk as elicited at the bedside and it was considered possible that these might be explained and others revealed in graphic records of the actual reflex contraction. It was with this in view that the present work was undertaken. It was necessary before starting to determine what stimulus must be given and how it can be graded, what the response to this stimulus could be expected to be and how it could be recorded and also what were the extraneous factors or conditions which could modify the reflex. The necessary conditions of recording dictated by these considerations are summarized in the following paragraphs.

THE EXCITABILITY OF THE MUSCLE.

All authorities are agreed that the muscle must be under some initial tension and that this tension must be partly active, i.e., no amount of passive stretch will produce the necessary tension background for a knee-jerk in the absence of all active contraction.

The presence of such a state of constant active contraction in the muscles of normal, healthy persons was suspected (Müller, Marshall Hall [54]), and even demonstrated in the frog (Brondgeest [10]) many years before the tendon reflexes were described, and although not mentioned by Erb (who, on the contrary, stated that the limb should be investigated so that all the muscles were slack) its importance is recognized by Westphal as an essential condition for the appearance of these reflexes.

All subsequent observers have given due recognition to its importance, but their emphasis has varied according to the view which they took as to the reflex or local origin of the tendon-jerk. Those who favoured the local-response theory were at pains to explain the obvious dependence of the tendon-jerks upon connections with the central nervous system, and found in the necessary presence of some tonic innervation an explanation of this dependence which allowed them to maintain their view that the response was a local one—the local irritability being itself dependent upon maintained connection with the nervous axis, and kept up either by the tonic contraction itself or by some necessarily associated means (Eulenberg [19], Zielien [7], Waller [90], de Watteville [92], Beevor [6], Gowers [32], Ferrier [22], Horsley [39]).

As a result of his researches upon the reflexes of the lower limb, in particular upon ankle-clonus, Hoffmann [35] has recently pointed out that voluntary innervation can in some cases bring out a reflex contraction to stretch not otherwise present. He suggests that it may of itself be sufficient to provide the necessary background of active tension upon which the tendon-jerk can appear in the absence of any normal muscle tone. Attempts have been made in the present work to obtain a tendon response from flaccid limbs in which steady active tension has been meanwhile produced by either voluntary effort or faradism of the motor nerve, but all have failed. In the absence of any further evidence in support of Hoffmann's suggestion it may be asserted that some degree of tonic innervation is an essential factor in the production of a tendon reflex.

The many conditions of disease in which the degree of muscle tone and the facility of eliciting the reflexes obviously go hand in hand are too well known to need emphasis—more important are those cases in which there is a discrepancy between these two, because the adequacy of the "local response" hypothesis stands or falls by this relation. It has been claimed, for example, by Foerster [23], that in some nuclear lesions and in some cases of lateral column affection the tendon response may be absent while the tone of the muscle is normally present or even increased; that in others, e.g., high spinal lesions, incomplete transverse spinal lesions and cerebellar lesions, the tendon-jerks may be increased while the tone is diminished or not demonstrably present at all; and that in the recovery stage of a cortical paraplegia the tendon-jerks reappear and become facile before any tone becomes appreciable. Lombard [48] considers that voluntary "reinforcement efforts" give increase of the tendon reflexes without increase of tone and provide another example of the same lack of correspondence.

It is, moreover, clear that so long as a certain measure of resistance to passive movements is taken as evidence of a corresponding degree of muscle tone, such discrepancies are bound to show themselves. Variations in purely peripheral, mechanical resistance, defective voluntary relaxation and that type of rigidity which has come to be regarded as associated with extrapyramidal cerebrospinal innervations all vitiate an accurate assessment of true muscle tone by purely manual manipulation, and the common practice is not to take the degree of muscle tone as indicating the probable condition of the tendon reflexes but to regard the facility of these reflexes as giving the most trustworthy indication of the presence and degree of tonic innervation. From these considerations it was clear that some means must be adopted for measuring the active and passive components of muscle tension.

THE NATURE AND SITE OF THE STIMULUS.

From the earliest description of the reflex the most effective mechanical stimulus was described as a short, sharp blow. Both Erb and Westphal stress this, and it is given prominence in the first important résumé of the knowledge of such phenomena by Petiglerc [62], who insists upon "un coup sec." They state, however, that such a blow may be expected in normal cases to give rise to the typical reflex contraction when applied at a variety of places—to the muscle, its tendon, the knee-joint and certain parts of the leg, especially over the subcutaneous surface of the tibia. That a blow in any of these situations may elicit contraction of the quadriceps was not in dispute, it was a matter of common observation, but a sharp difference of opinion as to the mechanism whereby these stimuli acted at once arose and still persists.

The joint capsule had a short-lived reputation as a possible receptor of the stimulus. Jendrassik [44] and Schreiber both claimed to have obtained typical contractions in dogs from hitting the joint capsule after this had been completely freed from surrounding tissues. This result was never substantiated under conditions which precluded a purely mechanical spread of disturbance to the muscle connections, and the notion of such "joint reflexes" has not survived.

The claim of the periosteum as a receptor has many adherents and demands much more attention. The idea that the contraction following a blow over the subcutaneous surface of the tibia was set up by direct stimulation of the periosteum was already presented by Erb in his original article. It was subscribed to by Strümpell [80] upon no very adequate grounds and vigorously championed by Sternberg, who performed a series of careful and detailed experiments in which the piece of bone whose periosteal envelope was struck was isolated by resecting a section of bone proximally to it, so that it remained connected with the rest of the limb and with the central nervous system only through the medium of certain soft tissues not under tension. He found that a blow upon this periosteum elicited a contraction in the muscle registered, claiming from this that periosteal reflexes had an independent existence apart from any stretching response.

This result was not repeated by any of the observers under such carefully controlled conditions, but those who deny to the periosteum any such rôle were many and emphatic in their scepticism.

Prevost and Waller [66], Gowers [32] and Hoffmann [35] held that stimuli applied over periosteum acted through a stretching of the muscle produced indirectly, either by a change in position of the bone struck or by a general transmitted vibration. Even the "radial periosteal reflex," allowed by all to occur, was said by Dumpert and Flick [17] to be absent when the fore-arm was supported, so that even slight extension of the elbow due to the blow was prevented. Yet as recently as 1927 we find Foerster [23] coming into the field as a staunch protagonist of the other view and supporting Sternberg in his contention. He claims that the last statement is incorrect: that, moreover, with regard to this particular reflex it can be elicited with the fore-arm in complete supination, so that the blow does not tend to extend the elbow, and also even from the ulnar border of the radius in some cases (paradoxical triceps reflex) in which the biceps, which contracts, has been directly slackened by the stimulus. He supports his view by adducing as further evidence the facts that in spastic cases a blow over one bony prominence will give rise to contractions in a whole series of muscles, some of which at least must have been slackened and not stretched as a result, and that in another case, one of hemiplegia, in which he had de-afferented certain muscles on the afflicted side, a blow to the bone of the sound leg caused a widespread contraction of muscles on the hemiplegic side, some of which were de-afferented and cannot therefore have contracted in response to stretch.

But these arguments do not bear criticism.

It has not been established that the reflex muscular contraction is always limited strictly to the muscle stretched in those cases in which the stimulus provided nothing but stretch and no excitation of periosteum. Therefore when a limb is vibrated or moved in any way owing to a blow upon some periosteum, it cannot be reasonably asserted that the stretching thereby provided is not of itself sufficient to set up contraction in all those other muscles in which it is in fact observed, i.e., that there must be some other source of irradiated reflex. When the knee-jerk of a spastic patient is taken in the usual way, the adductor jerks which are so frequently seen may be due to movements which are transmitted via the pelvis, as stretch, to those muscles. But there is ample evidence (Bohme [9]) to support the view that the reflex set up by tapping the patellar tendon and stretching the quadriceps femoris spreads in the central nervous system to give contraction of these muscles and probably of others. Such a view accounts also for the occurrence of a paradoxical triceps reflex.

This is found predominantly in the cases of a nuclear lesion of the triceps innervation, and all of its appearances may be explained either on the grounds of irradiation within the central nervous system, the nuclear lesion preventing activation of the triceps, or in that the reflex setting (Schaltung) of the cord at the moment of stimulation is such as to favour reflex activation of the flexors rather than that of the extensors.

Foerster's argument from the case of hemiplegia in particular will not bear scrutiny, for Sherrington has shown that the possible contralateral reflexes which may be set up even by such a well-defined stimulus as electrical excitation of an afferent nerve-trunk, are so interchangeable that nothing may be deduced from the contralateral response to hitting some bony prominence of the limb.

We may conclude as a result of this, that it has not been shown that the periosteal reflex plays any part in producing contraction of the quadriceps femoris, and that the observations which were put forward in its support can be adequately explained in another way more in line with the other phenomena studied.

There remains for consideration the effect of the stimulus upon the muscle complex, i.e., the muscle with the patella and its tendon.

It is by a blow over the tendon that the reflex is commonly initiated; such a blow may be effective through stimulation of the overlying skin, of the tendon itself or of the muscles to which it is attached. Although Erb has shown that when the skin was picked up and struck no contraction resulted, Jendrassik [44] claimed to have elicited one in response to painful non-mechanical irritation of the skin, a contraction which, however, came on after a longer latent period and which he called a "pseudo-knee reflex."

The presence of nerves in the patellar tendon was first demonstrated by Sachs [73], although Rollet [71] had previously described them in that of the sterno-cutaneous muscle of the frog and obtained no contraction in response to their direct electrical stimulation. It was Tchirjew [84] who showed that the function of the tendon as an elastic connection between muscle and bone was sufficient to explain the effects of striking it, for contraction of the quadriceps resulted when the tendon, denervated by isolating it from skin and bone and crushing its line of connection with the muscle, was then stretched and struck. Schreiber completed the argument by substituting for the tendon a string tied to the lower end of the muscle without impairing in any way the response. Gowers [32] and Schultze [81] had both come to the same conclusion from their study of the tendo Achillis jerk. Jendrassik [44] and Rosenheim [72] were the sole dissentients from this view. The former claimed that a typical reflex could be elicited when the freed tendon attached to the slackened muscle was supported upon a board and hit. Rosenheim came somewhat prematurely to the conclusion that the whole tendon phenomena were not reflex because he claimed to have obtained similar contractions from electrical stimulation of the freed patellar tendon. Sternberg repeated the experiment of Jendrassik but failed to confirm the results.

Gowers appears to have been the first to point out that a blow upon the upper edge of the patella could elicit the typical contraction although with less ease than one on the tendon. That in certain cases a blow over the belly of the stretched muscle set up a response was also shown by Sternberg.

The immediate result common to effective stimulation at all these various sites was a sudden lengthening of the already stretched muscle, and holding this to be the adequate and necessary stimulus to contraction Gowers referred to the phenomenon as a myotatic reflex.

The Receptors of the Stimulus.

Since some initial tension in the muscle is essential for the response, it is impossible to determine whether normally the adequate stimulus is a sudden increase in length or one in tension.

It has comparatively recently been decided that of the various forms of nerve end-organ in the muscle, it is the Golgi tendon organ which initiates an afferent stimulus in response to sudden stretch or increase in tension. Hinsey [34] has shown these to be always associated with muscle fibres and not to exist in the tendon. With a muscle in a normal degree of tonic innervation these tendon organs are all constantly supplying afferent stimuli to the nervous system (Adrian [1])—the effect of the sudden stretch of the whole muscle produced via its tendon is to cause these to fire off maximally and synchronously—providing in normal cases sudden discharge of the motor neurones innervating the muscle in which they are situated; or in abnormal cases a series of such discharges not limited to the original muscle.

If the intramuscular receptors are paralysed by novocain, no reflex contraction to stretching can be elicited, and Foerster holds that the loss of the tendon reflexes in severe tabes dorsalis is in part at least due to anæsthesia of these receptors; for Mann and Schleier [51] have shown that in such cases stretching of the muscle produces no electrical response in the posterior roots.

It seemed, therefore, clear from a consideration of the nature and of the receptors of the stimulus that, provided some means were adopted of giving a sudden sharp stretch to the muscle itself, nothing else was achieved by percussing in any particular place, and that the amount and rapidity of this stretch determined a complete evaluation of the stimulus.

THE COURSE OF THE CONTRACTION.

With increasing vigour of the knee-jerk, there may be observed a gradation of the response commencing with a just palpable thickening of the vastus internus muscle, and, passing through various degrees of visible thickening of the whole quadriceps femoris, until a stage is reached in which shortening of the muscle with extension of the knee and a kick-up of the pendent foot is observed. As the strength of the response increases still further, the contraction spreads to other muscles, first ipsilateral and then crossed, the adductors being those which most frequently contracti

This irradiation of the response was not at first regarded as genuine—it was explained as being due to an irradiation of the stimulus through skeletal vibrations. Waller [90] found that the crossed adductor contraction in a rabbit was abolished after the femur of the stimulated limb had been broken across. Many others agreed that the widespread contractions were all parts of the response to the stretch of one muscle, and even used this view, while still a hypothesis, to substantiate their claim that the phenomenon in the particular muscle stretched must be reflex and not merely local (Hombrand, Dodge [16]). Most of the recent work (Hoffmann [35], Warder, Sherrington) supports the view that the impulses may spread in the central nervous system over neighbouring neurones and innervate them reflexly.

In the present observation it was decided to limit the recording of the response to that shown in the quadriceps femoris muscle, both because a particularly favourable means was found of leading off simultaneously from all the component parts of this through its tendon, and because it was the only muscle of which the tension could be accurately recorded. It was, however, recognized that contraction of the quadriceps alone was in some cases probably only a part of the total response.

THE ANATOMICAL MECHANISM.

Experiment and observation have together defined certain nervous connections of the muscle as being both necessary and sufficient for the establishment of the reflex. These comprise the receptors in the muscle itself, afferent and efferent components and certain parts of the central nervous axis.

The nature of the receptors has been dealt with in another section of this paper, but it may be pointed out here that Magnus and Liljestrand [52] have shown that the reflex can be abolished by cocainizing the muscle in such a way that its motor power to other forms of stimulus is undiminished, i.e., the receptors alone are affected. The fact that there is complete unanimity with regard to the other parts of the reflex arc makes their enumeration simple. The afferent impulses leave and the efferent impulses reach the muscle along the same nerve—the anterior crural. Sherrington has shown that in the cat the afferent fibres enter the cord through the third and fourth lumbar posterior roots, and that the efferent fibres emerge from the anterior horns of the fourth and fifth lumbar segments. The brevity of the latent period led workers (Hoffmann [35], Jolly [45]) on this subject very early to suggest that there are no intercalated neurones between these two sets of fibres, and later the estimation of the proportions of this delay which may be attributed to conduction within the cord supported their view; but the more recent work of Sherrington and his co-workers seems to indicate that some, at least, of the phenomena of these reflexes are more easily explained on the assumption that there are, at least, two synapses upon this part of the path.

The functional interruption of any of the paths above detailed is alone sufficient to abolish the reflex, as is also destruction of the corresponding segments of the cord. The reflexes persist in rabbits after total destruction of the cord two segments above this level (Waller [90]), so that it is clear that this mechanism is sufficient in itself to provide the reflex. Although no one has questioned this sufficiently it has been suggested that other higher centres may sometimes collaborate, Wertheim Salomonson [94] claims to have found evidence for a component of the reflex involving a centre in the brain in much the same way as Sherrington implicated a pre-spinal centre anterior to the pons in the production of a crossed extensor thrust in which the same muscle plays a predominant part. Whatever rôle such additions to the simple reflex arc may have, all are agreed that they are accessory and subordinate.

It is interesting in this morphological context to note that Waller observed, without explaining it, the fact that seventeen months after cutting the anterior crural nerve in a rabbit regeneration was complete, the tone and the voluntary innervation of the muscle appeared faultless, and yet the knee-jerk had not reappeared. Sherrington demonstrated that the reflex could be abolished not only by severing the posterior roots traversed by the afferent impulses but by merely diminishing their conductivity. Both of these observations are associated with one well known to the clinician, that with impairment of peripheral conduction, as in a neuritis, the tendon responses are early, and sometimes permanently, abolished, thus making them especially sensitive indicators of slight peripheral nerve damage.

THE NATURE OF MODIFYING INFLUENCES.

The association between tonic innervation of a muscle and its tendon reflex is so close that any apparent departure from this excites comment. That this tone is maintained reflexly through the central nervous system is universally allowed. The cases in which the tendon-jerk is present while muscle tone seems absent are not sufficiently well established to allow of their being used as conclusive evidence that the nervous connections are essential apart from the provision of tone.

The modification which the reflex undergoes with different changes in distant parts of the central nervous system, gross pathological lesions, cortical activity, &c., lends colour to the reflex theory in that most of these changes cannot be supposed to produce their effect outside the cerebrospinal axis itself.

It was frequently held by earlier observers that inhibition of the knee-jerk did not take place; de Watteville stated this and Erb had previously concluded that it could not be inhibited but only antagonized. Sherrington, however, clearly demonstrated the possibility of inhibition (*Proc. Roy. Soc.*, B 52), in 1892.

The phenomenon of reinforcement appears to have passed without dispute, although various untenable theories were put forward to explain its mechanism. Since its first description by Jendrassik [43], many authorities, including Mitchell and Lewis [55], Lombard [49], Bowditch and Warren [11], have investigated the conditions of its occurrence.

The question as to whether voluntary reinforcement efforts, when performed alone, give any shortening or increase of tone in the quadriceps has been variously answered by different authors. Lombard held that they did not; Golla [29] claims to have demonstrated shortening of the passively extended muscle brought about by either muscular or mental effort, and holds further that the increase in tone is proportional to the effort put forth; Lombard could find no increase in the excitability of the muscle to electrical stimulation during voluntary mechanical effort, so that there is no adequate explanation of reinforcement in terms of purely peripheral changes. Most authors attempt to bring its influence into line with the established fact that interruption of cortico-spinal paths above the lumbar segments leads to exaggeration of the knee-jerks, by assuming that some normally constant degree of innervation down these paths provides a steady level of inhibition over the local reflex centre, and that as a consequence of voluntary effort the essentially single-minded cerebrum becomes in some vague way preoccupied so that this inhibitory stream diminishes.

On the other hand a directly opposite view of the mechanism of reinforcement has been put forward by Hoffmann [36], Nonne [60], Karger and others. Hoffmann claims that the pyramidal tract carries facilitating stimuli, because with maximal voluntary relaxation the current of action of the tendon response is diminished, and with voluntary contraction of the muscle it is increased (see also Wacholder and Altenburger [89]), and the refractory period of the response is lessened. When the muscle is in voluntary contraction, he argues, although we may not be able to see the knee-jerk the fact that one actually supervenes upon an appropriate stimulus is clearly shown by the typical action current which follows, even when the quadriceps is being contracted powerfully against a resistance. He concludes, therefore, that during voluntary reinforcement efforts there is in some way an indiscriminate overflow of cortical activity increasing amongst other things this flow of facilitating impulses. Nonne [60] supports this view with the claim that in hysterical hemiplegia there is often a loss of tendon responses on the afflicted side, and that these appear when the condition clears up and voluntary movements return. Karger's contribution is the observation that during sleep and other states of diminished general innervation the knee-jerk is found to be absent.

V. Weizsacker [93], realizing no doubt the imperfect character of the explanations afforded by either of the above theories alone, came to the conclusion that the Jendrassik "Handgriff" acts either by making the muscle slack from inattention or by giving a slack muscle some "Mitinnervation," a conclusion which does not considerably further our understanding of the problem.

There are certain other indirect modifying influences to which the response is subject. The action of narcotics has been investigated by clinicians and experimental workers. Erb held that the response was uninfluenced by drugs; Horsley [39] pointed out that they survived the administration of nitrous oxide in anæsthetic doses after the cutaneous response had disappeared. Reinhard [69] found them abolished in deep chloroform anæsthesia, an observation confirmed by Eulenberg [19], who maintained that they were not similarly affected by ether. Asphyxial states abolished them (Eulenberg [19], Reinhard [69]), as did also coma (Sternberg [83]) from whatever cause. After sudden death a diminution in the reflex can be seen in one minute and it is rare for any response to survive for more than forty minutes. The knee-jerks, which persist indefinitely upon repeated stimulation when the subject is at rest and unfatigued, may disappear when a condition of general exhaustion follows strenuous over-activity (Dodge [16], Oekonomakis [61], Schenk and Wissemann [79], Brissaud [13], Marinian [53]). Allied with this disappearance is their absence after an epileptic fit (Beevor [6]) and in febrile conditions, especially in children (Bohme [9]). Other general influencing factors have been commented upon, such as the increase in the reflex on cooling by a cold bath (Beevor [6], Sternberg), or the simultaneous application of non-localized electrical stimuli to the limb (Sternberg, Levandowsky [46], Neuhof [59]).

This review of the different factors which are known to modify the knee-jerk suggests that we may expect it to be elicitable from a person with the quadriceps in a normal state of tonic innervation apart from any effort at voluntary activation of the limb. Mental attention and preoccupation must be stabilized as far as possible since quantitative measurement of these conditions is impracticable. The person from whom records were being taken was introduced to the conditions of the experiment, including the eliciting of general responses before any one of these was photographed. While each record was taken he was asked to watch the shadow thrown across the aperture of the camera and to notice its movement. This was suggested to the subject as being of interest to himself rather than of importance to the recorder.

The effects of general fatigue were avoided by recording from patients who had not been recently and strenuously active; the above evidence on this subject justified the assumption that the reflex itself suffers on repetition no degree of fatigue which would vitiate the comparison of successive records in a series of moderate length such as was here obtained.

That the reflex may be inhibited seems clear, and the disposition of the limb must be such that this inhibitory effect is minimal; comfort, voluntary relaxation and an unstretched position of the hamstrings are the chief conditions thereby dictated. The above summary of the modifying factors suggests that if these conditions are complied with no other peripheral changes occurring simultaneously with the effective stimulus need be taken into account as being likely to affect the response.

THE TIME RELATIONS.

Each part of the nervous pathway requires a certain minimal interval of time for its activation, and for the passage of the excitation through it to the succeeding component of the reflex arc. It is clear that the total latent period of the knee-jerk cannot be less than the sum of these two delay intervals.

The difference between the latencies of various tendon responses and between those of knee-jerks under different conditions should be explicable in terms of known variations in the component parts involved.

THE LATENT PERIOD.

The extreme quickness with which the muscular contraction appears to follow the stimulus has always excited comment and measurements of the latent period confirmed this. With increasing accuracy of recording, the instants at which the blow was delivered and the first sign of response shown in the muscle, it became harder and harder to reconcile the brevity of the interval which separated them with conduction through the reflex arc.

The beginning of the stimulus has always been the easier of the two events to record, that of the muscle response has required more ingenuity and has been subject to wider degrees of approximation. All mechanical records have been delayed by inertia not only of the apparatus but of the limb segment moved as contraction continued. Mechanical records of thickening have been less subject to error from either of these sources but still to some degree distorted by both. The most accurate methods have been those employing the breaking of an electrical circuit due to thickening of the thigh (Rosenheim [72]) or movement of the foot (Tuttle [86]).

With the introduction of sensitive galvanometers and the recording of action currents in muscles, a new series of values has been introduced. These are measured from the instant of the blow to the commencement of the action current, not to the beginning of contraction. The interval is in all cases smaller. This should be noted because it is uncertain what electrical changes are being sampled when electrodes are pushed into the muscle or laid upon the skin over its surface; not only does this "current of action" follow the blow in some cases in which no muscular contraction is visible or recorded, but there is no ground for the assumption that the electrical disturbance always necessarily precedes the contraction by the same interval of time.

The chief results of measurement of the latent period of the knee-jerk are summarized in the following table:—

LATENT PERIOD DETERMINATIONS.

Author	Method	Subject	L.P. in sigma
Gotch ..	Lengthening ..	Rabbit	5—8
Scheven ..	,, ..	,, ...	20
Waller ..	,, ..	,, ...	8
,, ..	,, ..	Human normal and pathological subjects	20—120
,, ..	Thickening ..	,, ,,	30—40
Purves Stewart	,, ..	,, ...	69—126
Tchirjew ..	— ..	Human pathological subjects	32—34
,, ..	— ..	,, normal subject	58—61
Brissaud ..	— ..	,, ,, ,, ...	48—52
,, ..	— ..	,, pathological subject	38—42
ter Meulen ..	— ..	,, normal subject	35—90
Sternberg ..	— ..	,, normal and pathological subject ..	less than 30
Rosenberg ..	— ..	,, ,, ,, ,, ...	25—60
,, ..	— ..	Rabbit	25—25
Gotch ..	— ..	Human normal and pathological subjects	25
James ..	— ..	,, ,, ,, ,, ...	25
Eulenberg ..	— ..	,, ,, ,, ,, ...	24
,, ..	— ..	,, pathological subject	less than 24
Jendrassik ..	— ..	,, normal ,, ...	23
de Watteville ..	— ..	,, ,, ,, ...	20
Gowers ..	— ..	,, ,, and pathological subjects	15—90
P. Hoffmann ..	Electrical ..	,, ,, subject	21—7
Jolly	,, ..	,, ,, ,, ...	21—3
F. A. Hoffmann	,, ..	,, ,, adult	19·6—23·8
,,	,, ..	,, ,, children	14·0—17·0
Snyder ..	,,	,, ,, subject	11·3

It appears clear that one is dealing with a response of which the latency is an important characteristic, that it is about 10—20 σ in normal cases, and that some means of recording must be adopted which will allow of time-interval measurements of this order. It has been stated that with increased facility of the response the latent period shortens, and that with other variations in stimulus or excitability it may lengthen, but the main problem is to determine what is the shortest interval which we shall be called upon to record and measure, i.e., what is the shortest latent period for which we have good evidence? It must be long enough to allow a disturbance to have passed through the nervous system and to have reached the muscle again.

The shortest recorded latent periods under well-controlled conditions were found by Snyder [82], who, photographing the shadow of the hammer as it fell on to the patellar tendon, and measuring from this moment to the beginning of the action current shown in leads adjusted as in Piper's experiments, obtained a value of 11·3 σ as his minimum. The accompanying table shows that this figure lies well below that of all other workers.

It is known that contraction frequently follows direct percussion over the main mass of a muscle, and it is important to determine if such an effect can in any way complicate or distort the true reflex response which we intend recording.

A comparison of these two types of response (see Appendix II) shows that their dissimilarity both in time and in form would make the recognition of distortion from this source quite simple should it occur, and that the direct local contraction can only be elicited from percussion over the body of the muscle and not from the aponeurosis or tendon.

METHOD AND APPARATUS EMPLOYED.

The conception of the knee-jerk as a fractional part of the general myotatic response to stretch shown by the vasto-crureus muscle will be seen (Appendix I) to depend upon a variety of data, partly clinical and partly experimental. It has already been pointed out that the clinical observations are open to more than one interpretation, and give in themselves no conclusive evidence in support of the reflex nature of the tendon responses. The experimental results which really substantiate this view are derived from a comparative study of the forms of mechanical contraction exhibited by the muscle in response to different stimuli, in particular those which follow varying degrees of passively produced stretch and direct electrical stimulation of the motor nerve.

The applicability of such results of experimental physiology to an understanding of variations in the human knee-jerk must remain a matter of surmise, however probable their validity may be, until comparable records have been obtained in adequately controlled circumstances from the reflexly contracting muscle in man.

The apparatus employed in obtaining the following results was devised in the attempt to obtain from intact human muscle in living subjects contraction records comparable with those already obtained from experimental animals whose muscles may be freed from their insertions and attached to some recording lever.

A full description of this apparatus and of its use may be found elsewhere [67A]. The advantages there claimed for this method are:—

(1) The smallness of the inertia and momentum of the moving system.

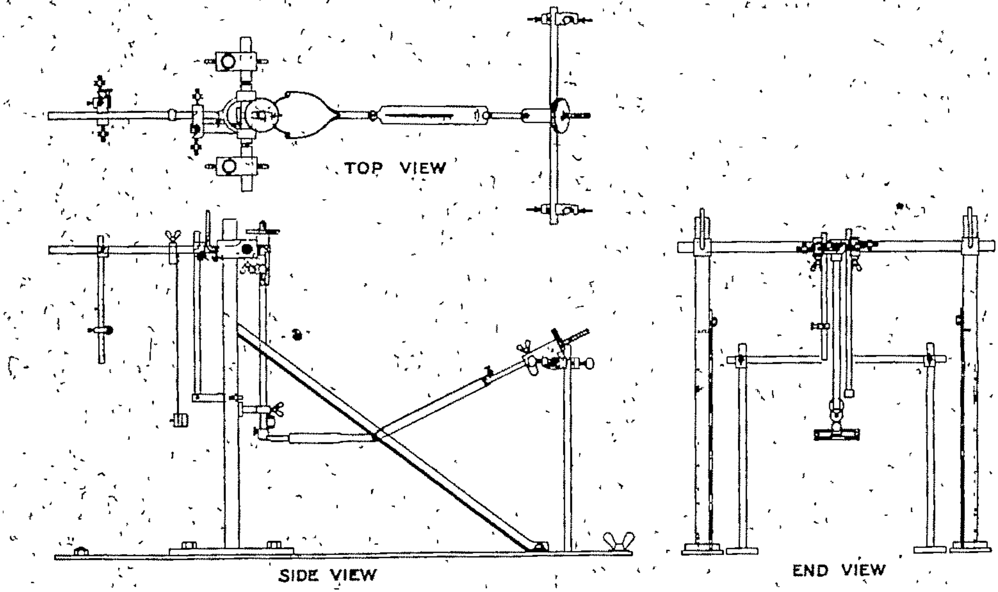


FIG. 1.—A line drawing of the apparatus used.

The subject sits upon a substantially built table clamped to a bar bolted through the wall. He reclines against an adjustable back rest and extends both legs along the table. The leg from which records are to be obtained is strapped firmly to a padded back-splint which is in turn bolted to the table in such a manner as to allow of its being raised and lowered but not moved in the axis of the limb. Two rigid, strutted vertical pillars, one on either side of the table, carry a horizontal member upon which is hinged a vertical bar free to swing in the direction of the table's length. This bar is extensible and its length controlled by a screw collar at the upper end. At its lower end it carries a piece of iron shaped like an undercut horseshoe, the lower end of which can be made to engage behind the upper border of the patella. At the foot of the table another horizontal bar supported upon vertical pillars carries a rod ending in a spring balance. The free end of the spring of the balance is connected to the horseshoe by means of a light aluminium frame. By means of a screw collar at the fixed end of the spring balance this can be drawn towards the foot of the table. Extending the spring and pulling down the patella provides any desired degree of tension in the quadriceps femoris muscle in whose tendon it lies. If the muscle is stimulated to contract under the above conditions the patella is pulled towards the head of the table against the tension of the spring, and the vertical bar carrying the horseshoe-shaped clamp rotates about the horizontal axis of its hinge. It is the movement of this bar which is recorded optically upon a falling photographic plate. To provide the necessary increment of tension or of length in the muscle for eliciting a knee-jerk, a rubber-faced hammer carried by a laminar spring was arranged to strike upon a circular metal plate fixed to the bar, whose movements are recorded. The upper end of this spring is movable along a horizontal support which carries also a catch for holding the spring in any required degree of deformation and releasing it at the right moment and a ratchet which is knocked over as the spring passes on its way to deliver the blow and which, catching it upon the rebound, prevents its giving more than a single blow transmitted to the patella. The impact of the hammer drives the horseshoe support towards the foot of the table, and thus gives a sudden stretch to the muscle.

(2) The functional isolation of the muscle which records independently of any other muscles.

(3) The ease with which the tension in the muscle may be adjusted and determined as a pull upon its natural attachment and in the functionally normal direction.

(4) Distances upon the record are directly proportional to changes in length of the muscle at all stages of contraction.

(5) It provides a comparatively close approximation to those experimental conditions under which similar work has previously been done on animals.

The photographic records obtained show the following characteristics:—

(1) A period of resting equilibrium with the muscle under some initial tension.

(2) A descent of the curve corresponding to sudden lengthening due to the blow provided.

(3) An ascent corresponding to contraction of the muscle.

(4) A plateau of maintained contraction.

(5) A descent of the curve following relaxation.

(6) In some cases, a series of after-contractions.

THE RESULTS OBTAINED.

Occurrence.—The material available consisted entirely of hospital patients, and was not suitable for any estimation of the percentage failure to elicit knee-jerks in otherwise normal subjects. Nothing remains to be added to the figures already arrived at by others from hundreds—in one case thousands—of persons.

It was found that the knee-jerk obtained in the usual way by percussion over the patellar tendon with the knee in a semiflexed position was present in many cases in which the "suprapatellar jerk" could not be elicited. The reverse was never found to be true. In general, the reflex excitability had to be higher before percussion over the upper border of the patella became adequate—it never failed to evoke a contraction when the tendon-jerk itself was more facile. These differences are probably due to the altered position of the limb in the two cases, i.e., semiflexion when the tendon is hit and full extension when the patella itself is struck. In the latter position the hamstrings are fully stretched and reflex inhibition from this source maximal; in the former they are relaxed and the inhibition very much less.

Two observations support this view. It is well recognized that the

Achilles jerk is always difficult and often impossible to obtain with the leg fully extended. In practice the knee is flexed before any attempt is made to evoke the reflex, and a clonus which has been established, and is continuing regularly in this position, almost invariably ceases immediately the knee is allowed to extend. Again, it was here found that in some cases in which percussion over the upper border of the patella failed to produce any response while the patient was sitting up, this became effective directly he was placed supine. This presumably achieved a similar relaxation of the hamstrings "from the other end," as it were, by extension of the hip. Unfortunately the discomfort of this position over an extended period did not allow of its being used as a routine when the patients were registering in the apparatus.

Facilitation.—No extended observations have been made upon this subject—the uncontrollable factors of attention, apprehension, general comfort, etc., were stabilized as much as possible at the beginning of each set of readings, and since they do not admit of quantitative variation and measurement no attempt was made to study their individual effects. In a few cases in which a series of responses had been elicited with ease and regularity, the subject was asked to make a forced grasping movement and the stimulus repeated. The curves show that when the response was not already maximal an increase in height followed this manœuvre, and when the excitability was low or the stimulus inadequate the addition of this voluntary movement to the other conditions raised the excitability sufficiently to make the stimulus adequate.

Inhibition.—The effect of reflex inhibition from extension of the hamstrings has already been mentioned. The only other form of inhibitory stimulus used was faradism of the ipsilateral popliteal nerve. This did give a very definite decrease in the excitability sufficient in some cases to extinguish a response otherwise present, and in others to produce a diminution in the height of the contraction observed.

Variations in stimulus and initial tension.—No response can be elicited from the non-extended muscle—some degree of background stretch is always necessary, and for normal subjects an initial tension of about 300 grm. wt. was required before any stimulus became effective. With increased facility of the response a lower initial tension sufficed—with average stimuli this decreased to about 100 grm. wt., or rather less—in some cases a sufficiently heavy blow evoked a contraction before the spring extension registered any pull at all. These were invariably cases associated with a considerable amount of spasticity and the presumption is that the active tonic activity of the muscle provided a background of reflex excitability sufficient for a heavy stimulus; in cases of less or of no pathological spasticity the actively developed tension had to be supplemented by greater degrees of passive pull before the excitability was raised sufficiently for any stimulus at all to be adequate.

It was rarely found possible to extinguish the response altogether in normal subjects by means of a very strong pull on the patella, but although high passive tension was in this way ineffective, cases were found in which the spasticity was so great that the muscle appeared to be already maximally contracted, no further contraction being observed when the patella was struck. In such cases a response in other muscles—e.g., the adductor of the same and of the other side—usually followed, and showed that the stimulus had set up a disturbance whose reflex effect was only occluded in those muscles already in maximal active contraction. These cases, further, were often those in which clonus was to be recorded as occurring either spontaneously or in response to the slightest added passive tension even when slowly applied.

When the initial tension was gradually increased in steps between 200 and 500—600 grm wt., and the force of the minimal adequate stimulus was measured, it was found that for such lower ranges of tension these two quantities were roughly in inverse proportion, i.e., as the initial tension was raised a smaller stimulus became effective. This may be explained in two ways. It may perhaps be that some minimal tension must be established in the muscle in order that the end organs should be stimulated and that this minimal tension is reached by the summation of the initial tension with the increment provided by the blow, so that when the initial tension is low the increment of tension must be greater and *vice versa*. On the other hand, it may be that the degree of reflex excitability which acts as a background for the response is increased progressively with rise of the initial tension, so that a smaller stimulus gradually becomes more effective. The evidence obtained from measurement of the curves favours the latter view, because when the initial tension is below the minimal value required for eliciting a response a very strong blow may be delivered and remain ineffectual. Yet the increment of tension which it provides, when added to that already present, gives a summed tension at the height of stimulation much greater than is actually effective on those occasions on which a very small blow gives a response when applied upon a background of slightly higher initial tension. Therefore the sum of initial and incremental tensions is not the value which determines if a response shall occur. Further it may be seen from the accompanying curves that the size of the contraction which results is determined in each case rather by the degree of tension background than by the force of the blow. With low initial tension the contraction is of less height and of longer duration than is the case with a higher initial tension, irrespective of the size of the blow, provided this be adequate.

The decrease in the size of the minimal effective stimulus as the initial tension increases cannot be attributed to the taking up of "slack" in the muscle or in its aponeurosis. This phase of slackness, if present at all in patients from whom a tendon-jerk can be elicited, lies far below the minimal degree of stretch at which a stimulus, however great, is adequate. Also over the range of increasing initial tension for which the above inverse relationship holds good, the passive tension and the degree of stretch which it provides vary in a way which clearly denies the presence of any such slack.

Thus we may infer that over a lower range of increasing initial tension the gradually increasing background of stretch reflex in operation produces a state of increasing central excitability which both makes a smaller stimulus effective and leads to a change in the character of contraction elicited. This change is from one of lower, longer duration to one of higher, shorter duration.

This is in accord with the results in cats obtained by Fulton and Liddell, and can be explained, according to Denny Brown [15], by the observation that with low central excitability the units of low threshold respond and that as this excitability increases proportionately more and more units of higher threshold become activated. The low threshold units, innervating as they do the slow red muscle fibres seen chiefly in the crureus part of the muscle, give the contraction of less height and longer duration which has been observed. The high threshold units innervate the pale, rapid muscle fibres which increase in proportion to the others as we pass through the different parts of the muscle from the crureus where they are minimal, through the vastus internus, the vastus lateralis to the rectus femoris, where their proportion is greatest; these pale, rapid fibres supply those higher contractions of shorter duration which are characteristic of the curves obtained at higher initial tensions. This is corroborated by the well-known fact that with low excitability and knee-jerks which are obtained only with difficulty, the first indications of a response are palpable, and later visible, contractions of the vastus internus of strength insufficient to raise the leg or change the position of the patella—just a momentary thickening of this part of the muscle. It is possible that the crureus (vastus intermedius) contracts minimally still earlier, but being nowhere subcutaneous its individual effect cannot be isolated by inspection or palpation. As the excitability of the reflex increases and the force of the contraction becomes greater the participation of other parts of the muscle-complex becomes obvious.

When curves are obtained from recording such contractions with increasing excitability the character of the jerk has been seen to change from the long, low type of curve to the quick, high type. This does not indicate that the units of low threshold and their slow, red muscle fibres which are activated with low reflex excitability fall out of operation as this increases, the higher units alone being reponsible for the contractions then obtained. They still contribute to the response, but since the form of the curve is dominated by the quicker elements the plateau remains flat and the angle sharp, and their contribution is probably only visible in the later stages of relaxation. That the response may remain isolated to the red slow units has been shown by Denny Brown for the cat, in which the composite parts of the muscle may be separately registered. There he found that when the units of high threshold alone are stimulated, the tendon-jerk as well as the response to slow stretch may spread from them to give response in the low threshold and slow red muscle fibre mechanism as well, but that the reverse spread does not happen.

It has been said that the above inverse relation between adequate stimulus and initial tension obtains over a certain range of lower tensions. At the upper limit of this range further increase in tension fails to lower the value of the minimal adequate stimulus and, in fact, with increasing degrees of initial tension the stimulus, to be effective, has to be further increased, until a tension is reached beyond which the jerk is completely occluded, however great the stimulus within the limits of tolerable painfulness.

This reversal of the relation between initial tension and stimulus may indicate that the contribution which passive tension can make to the central excitability is limited and that when its effect is maximal, and therefore also the potency of a given small stimulus greatest, any further increase in passive tension serves merely to make any constant additional increment relatively smaller and therefore increases the absolute size of that increment of tension (i.e., the stimulus) necessary to produce an effective lengthening The stretch units engaged in postural, reflex, tonic contraction will also be increased progressively in number and, since the size of the knee-jerk may be taken as a measure of the number of units still available for this postural contraction if further stretch is applied. (Denny Brown), if still more of the total number present in the vasto-crureus are already in action, i.e., if the central tension is still further increased, the numbers remaining available will become progressively diminished and the tendon response will again diminish in size. The stimulus will then have to be much increased in order to excite a sufficient number of the few remaining inactivated tendon organs.

One other allied observation made by Denny Brown has not been made in the present work. He found that in progressively stretching a composite muscle such as the vasto-crureus a tension was reached at which the tendon-jerk was completely occluded. When the tension was still further increased from this point the tendon-jerk occasionally reappeared; then the tension has to be very much further raised in order to make it disappear again. This he considered due to an unequal distribution of tension, and consequently of stretch background, in the different heads of the muscle; the tendon-jerk in the lower threshold heads becoming occluded before the excitability of those of higher threshold is reached. That such a sequence of events could never be detected in human subjects may be due to the pain which was caused by higher degrees of passive extension—this preventing a sufficient increase of the stretch necessary to render available the units of higher threshold. Much more probable is the assumption that there is in man no tension interval separating the units of low and high threshold, associated with the more complete mixing of pale and red muscle elements as well as more extensive differentiation of the muscle fibres themselves into pale elements.

THE LATENT PERIOD.

This has been found to vary considerably from one normal individual to another and within narrower limits with one subject at different times. The variations shown by the same person on different occasions, i.e., on different days, were less than the mean variation between different persons, i.e., each tended to have a characteristic average latent period about which the values obtained on different occasions varied slightly. From the series of normals examined no conclusions could be drawn as to the particular type of individual who tended to show a short rather than a long latent period. No evidence could be found for any shortening of this interval with increase of the stimulus or of the initial tension in the muscles. For any given person it appeared independent of both factors. Where facilitation was used to increase the size of a response no shortening of the latent period was observed. Again, in none of the records taken from patients with a variety of diseases of the central nervous system could any change in this delay-interval be made out to be characteristic of any particular lesion. Neither spastic cases nor hypotonic cases showed any typical changes common to the records obtained from either group.

The curve of ascent.—It has been pointed out earlier in this paper that the rising phase in the normal contraction record is mainly rectilinear. Generalizing this statement so as to include all the records obtained, it is found that this curve of ascent is sigmoid in shape, commencing at the point of departure from the underlying oscillation curve, with a diminishing concavity upwards which disappears completely as the curve becomes strictly linear. The curve remains linear for a varying distance until it is joined to the plateau by a part which is convex upwards. In the contraction curves obtained isometrically by Balliff, Fulton and Liddell [3] from isolated muscles, there is no strictly linear phase in the ascent, this being composed of only two parts, a preliminary concavity upwards which merges at the "point of inflexion" into the main part, which is then throughout convex upwards—this convexity gradually increasing until the plateau height is reached. It has been shown by these authors that the preliminary concavity upwards corresponds to that part of the contraction process in which the recruited muscle-units are overcoming internal friction and viscosity, and therefore that the duration of this phase will depend upon the rate and extent of recruitment, so that the lowness of the point of inflexion is a measure of the simultaneity with which the muscle fibres are stimulated.

It was found from the curves here obtained that when the same stimulus is applied with increasing amounts of initial tension the point which corresponds with this angle of inflexion, i.e., the point where the ascent first becomes rectilinear, occurs progressively earlier and that this change is still more marked when the initial tension is kept constant, and the size of the stimulus is increased. This would appear to suggest that simultaneity of stimulation of the muscle fibres is favoured by an increase both of the stretch background and of the size of the stimulus. Regarding the knee-jerk as the result of a sudden synchronism of the afferent units already activated by the preliminary passive stretch of the muscle, it is to be expected that both the above effects will be shown; because with increase of the background stretch there will be many more stretch units in action and the number of afferent impulses per second will be increased, so that more of these will be thrown with synchronism by the same sudden additional stretch. Increase of the stimulus means that the hammer is travelling faster when the blow is delivered, so that more units will be effectively stimulated in a shorter time. The effect of the background stretch is seen not only as the initial passive tension is varied in a normal individual, but also as the active component of the tension fluctuated in different subjects. Comparing the curves obtained with the same passive initial tension and the same stimulus from different persons, we find that in cases of well-developed spasticity the angle of inflexion is lower than in the normal, while in hypotonic cases it is higher.

The linear portion of the ascent curve which is normally present is seen also in spastic cases, but tends to be characteristically absent in hypotonic cases, in which it suffers diminution by being encroached upon both by the preliminary concavity and by the final convexity, upwards. In these hypotonic cases the convexity begins earlier and is much less sharp, being associated, as we shall later see, with absence of any true plateau.

From those records which show a well-marked linear rise it is possible accurately to measure the slope, i.e., the amount of shortening and of tension development per unit interval of time. In the table where this is recorded the slope is given in millimetres of shortening per sigma. Variations in this slope have been compared with those of the corresponding slopes of relaxation of the same records and with changes in the height of the curve. It has been found that as the stimulus is increased with constant initial tension and the total height becomes greater, the ascent slope becomes more nearly perpendicular, and that in general the same change occurs with increase in central excitability, i.e., the slope of the rise in spastic cases is greater than in normal cases: with diminution in the excitability it is less. It is less also in cases of Parkinsonian (extrapyramidal) rigidity.

In all these cases there is no correlation between the slopes of contraction and relaxation. If increase of the passive initial tension provided merely an increased tendency towards passive extension of the muscle, then the load against which the muscle contracted would be greater, and the restoring force providing relaxation when contraction had ceased would be increased. An inverse relation between the slopes of contraction and relaxation would, therefore, be expected. Such, however, is not the case and, in fact, as the initial tension increases over a certain lower range with constant stimulus the slopes both of relaxation and of contraction become greater, i.e., those parts of the curve become more nearly perpendicular to the base line. This also bears out the supposition that increase of the background of stretch activity provides a greater degree of simultaneity of activation and hence more rapid contraction. The total height of the curve is more properly a function of the ascent phase than of the plateau, it is a measure of the degree of contraction. It increases with increase of the stimulus, as would be expected. With constant stimulus and rising initial tension it at first increases and later decreases. The range of initial tensions over which this increase of height continues is the same as that over which an addition to the stimulus will heighten the response, i.e., it is the range over which increased simultaneity results from an increase of the background of stretch activity. Beyond this range the height of contraction decreases with rising initial tension, both because of the effect of loading in diminishing the extent of contraction in a given time, and because more and more motor units become occupied in full "postural" activity against the background tension, and fewer remain available for increasing the contraction still further when the jerk is elicited. Over this range, the size of the knee-jerk is, in fact, a true measure of the number of motor units still available for either the tendon reflex or further postural contraction (Denny Brown).

The plateau.—The curves of contraction and of relaxation are normally joined by a horizontal plateau of varying extent. The characteristics of such a plateau are its flatness, its duration and the sharpness of the angle by which it is ended.

The flatness must correspond to a period of maintained shortening in those fibres which have already contracted—it is clear that the apparatus can contribute nothing to this feature, and that in fact all the forces at work outside the muscle tend towards its disturbance. The records taken from any one person show that this characteristic tends to be better marked when the initial tension is higher—this also is an effect which follows from the increased simultaneity of contraction in the muscle fibres provided by a higher background of reflex stretch activity. The same increase of flatness of the plateau is seen when the tension is constant and the size of the contraction raised by increasing the stimulus, and the mechanism of these effects is probably identical.

It is a variation in the plateau which has been found to be one of the most constant characteristics of certain types of disease of the central nervous system. In spastic cases it is invariably well marked and can be relied upon to appear with certainty even in smaller responses. In hypotonic cases there is seen a rounding of this part of the record which may be so complete that no true plateau can be said to exist at all. A similar rounding is seen in cases of severe Parkinsonian rigidity, but never to the same extent as in hypotonic cases.

The duration of the plateau does not alter characteristically with responses of the same height from different persons with comparable degrees of reflex excitability, but two constant forms of variation can be seen. In the same individual the duration of the plateau decreases as the height of the contraction is increased and becomes shortest when this is maximal. In two different normal persons, if the stimulus required to elicit a response of a given height is greater in one than in the other, then the plateau will be shorter in the curve obtained with the greater stimulus. This probably means that in the person whose reflex is more easily elicited by a smaller stimulus more units of lower threshold are activated and the curve is produced mainly by slow red muscle fibres which provide a longer plateau. This is borne out by the observation that the two curves of the same height as above obtained have other differences which can be traced to the same origin, e.g., the angle of inflexion is higher and the slope of ascent less steep in the curve with the longer plateau.

In animals Fulton [25] described a flat plateau terminating in a sharp angle for both the muscle twitch and isometrically recorded knee-jerk, and further said that "It seems probable that a muscle allowed to shorten isotonically also exhibits a flat top and a characteristic angle." He showed from his records that the duration of the plateau of the isometric knee-jerk increases with increase of the initial tension, and confirmed Lucas's [50] findings that the plateau is of longer duration in the case of the knee-jerk than of the muscle twitch and longer in the case of submaximal than maximal response (Fulton [26]).

In the majority of records from normal persons the angle which ends the plateau is well marked and abrupt. It is present whether the response be maximal or submaximal, of the high short plateau or the low long plateau variety, but is usually better marked in the former. In all the records taken it is seen best in the muscle twitch elicited by stimulation with a break shock over the motor-point, and it is lost in all those cases in which the plateau is not in evidence. Fulton holds that since "contractile energy ceases at the angle," its sharpness may be taken as a measure of the simultaneity of relaxation of the muscle fibres. Its association in this series of records with a low point of inflexion on the curve of ascent and a fairly abrupt junction between the linear ascent curve and the plateau bears out this view, as does also the still greater acuteness of the angle obtained from the motor twitch.

The curve of relaxation.—Following the angle, the descent from the plateau is normally linear for the greater part of relaxation, merging fairly abruptly into the base line. The strictly linear part of the curve is better seen in relaxation from curves of greater amplitude, i.e., from plateaux of greater height, but it is almost invariably true to describe this part of the record as being normally always concave away from the base line except where the slope is constant. If we agree with the above recorded observations of Fulton, that "contractile energy ceases at the angle," we may assume that the course of relaxation is determined by the passive force tending towards extension as provided by the spring of the balance used, and opposed by the internal friction and viscosity of the muscle. This we should expect to provide a slightly accelerated curve if the extending force were constant, but since the record is not strictly isotonic this force falls off slightly but progressively with increasing extension and the accelerated character of the fall is lost. It is clear that in the final degree of extension at which further relaxation is arrested the extending force is opposed not only by the above internal resistance but by the tonic postural contraction of the muscle. It is this force which provides the terminal concave part of the curve of relaxation and brings the system to rest at the original base line.

In most of the records the resting length of the muscle was the same before and after the jerk, and any departures from this retention of resting length were in the upward direction, i.e., the curve did not fall quite to the original level but remained slightly above it. This was first interpreted as being due to an imperfection of the apparatus which allowed some alteration of the relative positions of the patella and of the frame which was attached to it. Since this, however, would be more likely to lead to a slipping of the frame towards the foot in which direction it was pulled by the spring, it is more probable that some explanation along the line suggested by Veits can better account for this slight increase of the maintained contraction when it occurs. This author found that there is an optimum set of tonically innervated muscle, and that following the subsidence of a clonic contraction there may be a readjustment of the length in the direction of this "optimum set," unless this was previously present, leading to a maintained slight shortening or slight excess lengthening.

The total duration of lengthening did not vary consistently in any way with the size of the response in normal persons, but it showed a definite decrease characteristic of hypotonic cases, and an increase in those of extrapyramidal (Parkinsonian) rigidity. Variations from the normal linear curve of relaxation were of two types. The first occurred in those cases of hypotonus in which, associated with an abnormal curve of contraction and the absence of any true plateau, there was found a sigmoid curve of relaxation in which a strictly linear phase was absent or minimal. The other type of variation produced a record of which the descent was convex upwards for its greater part and the concave terminal phase followed directly upon this initial convexity. This holding-up of relaxation obscured the "angle" at the end of the plateau, but that it was not due to increased asynchronism of the motor units innervated was shown by its occurrence invariably in curves of which the ascent and plateau were in every way normal. It was seen in records from normal persons only under exceptional conditions, but was characteristic of those from cases of spasticity associated with pyramidal tract lesions. Its nature is clearly revealed by the circumstances in which it was produced.

In cases of slight spasticity with increased facility of the tension reflexes a response could be elicited and recorded at low initial tension of the muscle which was in every way normal, the curve of relaxation being strictly linear. If responses were recorded with progressively increasing tension it was found that the convexity or delay of relaxation appeared and became gradually more pronounced. With an increase of this feature there appeared definite, small after-contractions, either delaying the later parts of the relaxation curve or being added on to the curve after relaxation was complete. With further increase of the initial tension these increased in size and total number until in favourable cases a single stimulus sufficed to elicit not only the initial contraction with a plateau of normal height and flatness, but also a series of indefinitely persisting after-contractions which occurred at a regular rate. Clonus had been established. Measurement of such records showed that the convexity upon the curve of relaxation preceded the first clonic contraction by the same interval as separated each beat of the clonic series. It appears reasonable to assume, therefore, that its appearance is due to the same factor which, when more pronounced, leads to persistent clonus. It is thus probable that it is not a persistent tonic after-effect tending to maintain shortening at plateau height, but is a clonic or phasic element occurring in these records immediately after the plateau and the same as the "hump" of Balliff, Fulton and

Liddell [28], or the "nose" of Fulton [27]. Its presence is associated with increased facility and hence with increased height of the response, is characteristic of spastic individuals and always precedes the appearance of a persistent clonus.

Clonus.—In some persons an optimum initial tension can be found at which a single blow will elicit a knee-jerk followed by a rhythmic series of contractions which persist as long as the tension is maintained. The average rate of this clonus was found to be about 8·5 sec. The rhythm was perfectly regular for any one person so long as other circumstances were not altered, and although at its inception there was a gradual increase in amplitude during the first few contractions, the rate did not similarly increase; nor did it later decrease in those cases in which the clonus desisted spontaneously. In the cases observed such clonus was only found where the tone of the quadriceps was quite definitely raised to passive manipulation, and clinical spasticity was well marked. When this spasticity was extreme it was often found possible to bring it out by a steady stretch of the muscle and in a few persons clonus alternated with periods of spastic contraction while the limb was lying free upon the experimental table. As a general rule the higher the degree of spasticity present and the greater the facility with which clonus was elicited, the more rapid was its rate, but a rhythm of more than 12 sec. was not seen. Since the limits of initial tension between which persistent clonus could be evoked were narrow it was not possible to state definitely that the rate was uninfluenced by the tension present, but this was certainly the impression received from observations made. It was invariably found that a slightly painful stimulus to the sole or skin of the same leg abolished it when once established. Attempts were made to facilitate its appearance by passive dorsal-flexion of the ankle, since it had been found that in some cases the tone of the quadriceps may be thereby definitely increased as in the Stutzreaktion of reflex standing [67], but no change was observed as a result of this manœuvre. The fact that it appears in those cases of which records at a lower initial tension are characterized by a "hump" upon the curve of descent suggests that it arises from an exaggeration of the same process to which the hump itself is due, and the time relations show that the hump may be regarded as the first of an abortive series of clonic contractions.

The relation of clonus to the knee-jerk has always attracted attention, and a tendency to regard the underlying mechanism as identical has gradually emerged. Before the tendon reflexes were themselves described, ankle-clonus occurring spontaneously had been studied by Brown-Séquard and, as evoked by a sudden stretch, had been applied clinically under the description of "épilepsie spinale" by Charcot and his co-workers. In his original paper Erb showed that knee-clonus could be elicited in favourable cases by depressing the patella from above, but he regarded this as being a distinct type of response not to be confused with "a knee-jerk of clonic form." Sternberg in commenting upon the phenomena considered it to be a rhythmic response of stretched muscle of which the relation to the knee-jerk was not clear. He attributed it to the working of some preformed, central mechanism for rhythmic reflexes, and describes it as being probably a spinal form of the tension reflex.

Many observers have since studied the conditions under which it arises and the rate at which it occurs. Veits, working with cats, considered it to be characteristic of decerebrate and not of spine preparations; although it could be elicited in spinal cats by means of the facilitating influence provided by stimulation of the crossed peroneal nerve. These observations referred to the clonus which followed a simple knee-jerk elicited in the ordinary way by a blow, i.e., a persistent clonic after-discharge, which he did not regard as of the same origin as the spontaneous clonus which he found to occur in spinal as well as in decerebrate preparations. The knee-clonus following a tendon-jerk in cats he found to be established at a rhythm of about 11·5 sec. In man the rate was lower—about 8·8 to 9·7 sec. In discussing its mechanism and the supposed tendency of the motor centres to rhythmical discharge, he pointed out that it has nothing to do with stepping movements, for these proceeded at a much slower rate, and that if clonus were simultaneously established in both quadriceps the contractions on the two sides were synchronous and not alternate. He found that for any one preparation the limits of the "tone" (? active muscle tension) between which it could be elicited were narrow, and included that assumed "optimum set" of the muscle to which reference has previously been made.

From his simultaneous electrical and mechanical records of ankle-clonus, Wertheim Salomonson [94] concluded that it was a series of simple muscle twitches, each preceded by a single current of action which tended to occur under conditions of increased muscle irritability and a certain degree of tonic contraction. He timed the first few of the series of contractions, and found the second beat to occur only 0·25 to 0·3 sec. after the blow was delivered. On measuring the duration of the first contraction he found this to be 0·2 to 0·3 sec., but did not go on from this to deduce any other relation between the initial and subsequent contractions. Sherrington held that "the stretch eliciting clonus can be regarded as one temporarily relieved by each contraction of the muscle itself and becoming operative again as each contraction subsides," i.e., each beat of the clonus is set up by renewed stretch during relaxation from the previous beat. A more accurate analysis of the electrical and mechanical records of the muscle in clonus now shows this view to be untenable.

Denny Brown [15] describes the phenomenon as a regular synchronous discharge which, while being most commonly set up by a tendon-jerk, is often seen to occur spontaneously in preparations with well-developed decerebrate rigidity, in which case also there may be seen spontaneously alternating phases of tonic and clonic activity. His records show a series of twitches in varying degrees of fusion accompanied by regular, large action currents. He finds that its appearance is favoured by allowing greater shortening during contraction, since the plateau after action is thereby reduced and relaxation increased, and also by the presence of a highly developed, stretch-reflex background. The optimum tension that provides this strength reflex must be partly active, for a certain degree of tension organ excitation is necessary to provide the proprioceptive inhibition which in his view determines the appearance of clonus. With higher degrees of tension background the individual twitches suffer greater fusion and the simultaneous action currents occur proportionately earlier and earlier until they can be shown to occupy such a place on the curve that the wave of afferent impulses to which each is due must have originated peripherally before relaxation from the previous beat commenced. Regarding, as Denny Brown does, this afferent volley as being set up by tension in the muscle fibres, it may be expected to arise at the period of greatest tension change, i.e., during contraction and relaxation. The afferent volley, therefore, which finally overcomes the barrier of proprioceptive inhibition and leads to the discharge of a further large efferent disturbance, cannot have been set up by the previous relaxation which occurs in many cases later than this action current, and must have originated in the previous contraction phase, or even partially during relaxation from the still further preceding clonic beat. The view that the action currents represent in this way a series of rebounds from proprioceptive inhibition explains the value of a tendon-jerk for their initiation, and the presence of a hump upon the curve of relaxation at lower tensions can be understood as being indicative of a tendency to clonus at higher tensions, since it merely gives evidence of simultaneity of relaxation in a majority of the units activated. This author finds that there is a special predisposition to clonus in the "spinal" state, where perfectly regular rhythms may be present at quite low tensions.

This fascinating study by Denny Brown of clonus as a form of discharge set up and maintained by a myotatic mechanism and dependent upon rhythmic release from inhibition of the spinal centres, shows us that the very first description of this phenomenon as "épilepsie spinale" was not as inadequate as the plausible, but really unsound, explanation which later supplanted it.

THE CHARACTERISTICS OF DIFFERENT VARIETIES OF KNEE-JERK.

Pyramidal tract lesions.—The changes typical of records obtained from such cases may show themselves to be unmistakably present at a stage of the disease when clinical examination reveals no demonstrable spastic resistance to passive movement. There is increased facility of the reflex shown by its appearance with both lower initial tension and smaller stimulus than normal. For the same values of tension and stimulus the response is of greater amplitude, it has a more nearly perpendicular curve of ascent, invariably a well-marked flat plateau and the curve of relaxation shows a preliminary convexity or hump which may be followed by one or more secondary clonic contractions.

No characteristic differences have been found to distinguish the responses occurring with lesions at different levels of the pyramidal tracts, but it may be stated as a generalization that their common characteristics are better emphasized in spinal cases than in decerebrate cases (hemiplegia, etc.), i.e., the amplitude is on the whole greater, the hump better marked, and the tendency to clonus more definite. This is in accord with some but not all of the results obtained from a comparison of the spinal and decerebrate tendon reflex in animals. Thus Balliff, Fulton and Liddell [3] found that the latency was greater in the case of the spinal knee-jerk, the requisite initial tension or adequate stimulus was larger, the total duration of the response longer, the point of inflexion on the ascent was higher and the curve of relaxation showed no hump. Sherrington agrees that the spinal reflex has a higher threshold for stimulation. Denny Brown and Liddell have shown that some stimuli which can inhibit the spinal supraspinatus jerk are weaker than those requisite for inhibition of the jerk in decerebrate preparations, while Cooper and Adrian agree that the after-discharge which they found characteristic of the decerebrate jerk is absent from the spinal jerk. In his most recent paper Denny Brown finds that the "spinal state" predisposes more than any other nervous condition to the presentation of clonus "at almost all tensions," and the hump which "indicates a tendency to clonus" would there be expected to be well marked, so that the evidence of comparatively recent work is not unequivocal.

Hypotonic cases.—There is in general an increased difficulty in obtaining a response from such cases which may amount to complete absence of the jerk. But this is not always so, and in some persons in whom the resistance to passive movement is minimal and the limb almost flail-like on shaking, quite good reflexes can be obtained. This may be in part associated with the hypotonicity of the flexors as well as of the extensors, so that the position of full extension of the knee which is adopted for recording does not set up so much stretch response in the hamstrings, and these therefore exert less than the normal inhibitory effect upon the appearance of a knee-jerk.

Many of the persons from whom records have been taken have shown typical "pendular" knee-jerks when these are elicited with the patient sitting upon a table and the legs hanging freely. Such "pendular" responses have always been held to be due to an absence of the normal participation of the hamstrings in determining the extent and form of the response. That the tension in the hamstrings normally increases during the knee-jerk when this is produced in the ordinary way is easily recognized even by palpation, but the relation of this increase of tension to the other concurrent events has been a matter of much dispute. Pfahl [64] held that these muscles contracted secondarily to their stretch as the knee was extended by the reflexly contracting quadriceps. Lombard [48] considered that the original stimulus—stretch of the quadriceps—provides reflexly contraction not only of that muscle but also, somewhat later, of the hamstrings. This interval between the two antagonistic contractions has been measured by Golla and Hettwer, who arrived at a value of seven sigma. Lombard further attributed the short jerky clonic reflexes which occurred especially towards the beginning of any one series of responses to the too early contraction of the flexors. Sherrington has put forward the suggestion that the hamstrings exert not only a mechanical braking effect upon the "hanging knee-jerk" (which can be diminished by denervating them and making them toneless) but also that impulses set up in the tonically innervated flexors, consequent upon their stretch during the early stages of knee extension, react by inhibition upon the quadriceps, affecting the later part of the response. This part of the effect can be destroyed by deafferenting them, and in corroboration he cites the well-known fact that the Achilles jerk is more easily obtained when the knee is bent, i.e., when the hamstrings are relaxed.

The position of the leg and the nature of the events recorded in the present experiments, by purposely precluding all effects of the hamstrings, make it impossible to determine their behaviour during the contraction of the quadriceps, but the curves obtained show that the form of the contraction in the quadriceps alone is sufficient to account for the pendular type of response. Those curves are characteristically dome-shaped, a sigmoid curve of contraction passing over into a similar sigmoid curve of relaxation without any tendency to the formation of a plateau. The absence of any linear phase in the ascent makes it impossible to obtain comparable values for the slope of this part of the curve, but it does not appear to be markedly abnormal. The slope of the fall, however, although nowhere linear, does show an increased, general steepness of this part of the curve. The whole curve suggests a complete absence of maintained contraction and of synchronism in the individual muscle-fibres. This type of response, found here in association with unilateral cerebellar lesions, in the limbs of the same side, appears to be produced by a sudden, short-lasting, jerky contraction with an absence of maintained shortening which may be closely allied to the spasmodic contractions and lack of postural fixation shown by Holmes [37] to be clinically characteristic of such cases.

Chorea.—The knee-jerks in this disease are notoriously variable; not only are they exaggerated in some cases and lost in others not otherwise dissimilar, but in the same patient successive blows may yield totally different results without the conditions having appreciably changed. This may be in part due to the constantly varying amount of voluntary innervation and relaxation associated with the restlessness characteristic of such patients.

Apart, however, from the ease or difficulty of eliciting a response, the jerk, when it appears, frequently shows another variation. It has been described as the "sustained" knee-jerk of chorea. This may clearly be due either to an extension of the plateau in the form of persistent tonic after-effect or to the secondary addition of either clonic or voluntary contractions.

Wertheim Salomonson, recording such a jerk both electrically and mechanically, came to the conclusion that it was composed of a preliminary simple muscle twitch to which was fused a true tetanic contraction of varying duration and a latency of 0·21—0·25 second. He suggested that chorea was one of the conditions in which some cerebral reflex centre was called abnormally into operation, the area of stimulus-reception being the skin around the patella, and the response the tetanic contraction observed.

In the records here obtained abnormal responses have been found in such cases to show two additions to the preliminary twitch, a definite prolongation of the response and the occurrence of secondary contractions. The twitch itself was frequently of the hypotonic variety with no plateau. The prolongation was not present as a plateau of much increased duration but as an abnormally delayed descent; both this prolongation and the secondary contractions do not show the same time-relations and characteristic form of the clonic elements found in spastic cases, but are larger and more spaced out. In addition, some records have shown what is undoubtedly a voluntary contraction following comparatively long after relaxation has been completed.

Extrapyramidal (Parkinsonian) rigidity.—It was, in general, found difficult to predict the degree of facility which would be shown by the reflex from a consideration of the amount of rigidity present, but as a rule it tended to show a facility which was maximal for the first few jerks elicited and thereafter to become much more refractory. It was found impossible to stabilize the amount of voluntary relaxation sufficiently for a series of constant contractions to be obtained, so that any conclusions as to their variability with different initial tensions and different strengths of stimulus would be unjustified. In this extreme, apparently spontaneous, variability of the response these cases resembled those of chorea. The curve of contraction obtained was characteristically rounded with no plateau, no trace of a terminal "angle" and a delayed descent followed by a very slow return to the previous base line of resting equilibrium.

SUMMARY.

This paper is concerned with an attempt to examine and record the knee-jerk in man, in order to find what are the changes in this reflex typical of different diseases of the central nervous system.

A short account is given of those changes which have hitherto been recognized as appearing under such conditions. From these isolated facts of clinical observation generalization is only possible in the light of the accepted physiology of the reflex.

A summary is given of the current physiological conception of the knee-jerk as a reflex rather than as a local muscular response, and its explanation as a particular example of the general myotatic stretch reflex is adopted as the most satisfactory. The work upon which this view of the reflex is based has been done by other workers in carefully controlled experiments upon animals, and for testing its validity in the case of the human knee-jerk the conditions of recording from man must be approximated as closely as possible to those of the above experiments. It is shown that previous methods of recording the human knee-jerk failed in this respect, and it is claimed that the apparatus and method here described present a definite advance in this direction.

The calibration and errors of this apparatus are discussed and examples of the records obtained by its use are given. Inspection and measurement of these records show that the essential form of the reflex is the same for both man and animals, they reproduce the characteristics of the curves obtained from rabbits and cats, and the typical features of decerebrate and spinal responses are seen to be identical in both.

In this way the applicability of physiological data to the human knee-jerk is confirmed, and in so far as the above view of the nature of the reflex is valid the explanation of the phenomena of human muscle tone and spasticity in terms of myotatic stretch response is justified.

In addition, this method provides possibilities of detecting and recording changes in form of the reflex which are of definite clinical significance. Many of these changes are shown to characterize certain lesions of the central nervous system and their existence to be of diagnostic value. In particular those changes typical of interruption of the pyramidal tract at different levels, of extrapyramidal (Parkinsonian) rigidity, of cerebellar disease and of chorea are summarized and the occurrence and significance of clonus discussed.

This work was made possible in its earlier stages by the facilities very kindly afforded by Sir Thomas Lewis who allowed it to be carried on for a time in his department and whose technician is responsible for building most of the apparatus. I am glad to acknowledge my indebtedness also to the Physicians of the National Hospital, Queen Square, for permission to use records obtained from patients under their care in that institution; to Dr. F. M. R. Walshe, in charge of the Neurological Department at University College Hospital, for his advice and encouragement throughout; and to Dr. Denny Brown for his helpful discussion of many points.

APPENDIX I.

THE KNEE-JERK AS A MYOTATIC REFLEX.

From the above detailed considerations it appears that the knee-jerk is in its simplest form a contraction of the quadriceps femoris muscle evoked by a sudden stretch. This response is conditioned by the functional activity of certain nervous connections of the muscle and of that part of the spinal cord with which these are associated. It can be modified indirectly by a variety of factors—lesions of the central nervous system, drugs, etc., and can be both facilitated and inhibited centrally. There is always a short interval between the delivery of the stimulus and the beginning of the response, i.e., a latent period.

In all these ways it possesses those attributes which are characteristic of a true reflex, and it contrasts in several definite particulars with what is known to be a direct muscle response, dependent upon local excitability.

Measurements of the latent period show this to be very short, and transmission of the disturbance initiated by the stimulus through the nervous system and back to the muscle can only be reconciled with these measurements if the rate of conduction along the nervous pathways has the highest value which has been suggested for it.

Since the balance of the above evidence suggests that the knee-jerk is to be regarded as a true reflex contraction set up in response to stretch of the muscle itself, it is of interest to examine how this particular reflex compares with or differs from the other known stretch reflexes shown by the same muscle group.

In 1924, Liddell and Sherrington [47] published the result of their investigations into the behaviour of muscles when stretched. They found that a muscle deprived of nervous connections reacted when slowly stretched as would a partly viscous, partly elastic solid of the same dimensions. When fully innervated, it behaved very differently. Such a muscle when slowly and progressively stretched responded by developing additional tension, which continued to increase so long as the muscle was being lengthened, preserved its increase so long as the new length was maintained, and decreased immediately the muscle was allowed to shorten again. The characteristic features of this response were the readiness with which the muscle reacted to minimal degrees of stretch, as small as 0·8 per cent. of the total length, a latent period amounting to some interval less than 20, and its dead-beat nature, i.e., the immediate fall in tension which followed either shortening or inhibition with hardly any after discharge.

Whatever the length of such an innervated muscle, these reactions—i.e., an increase of tension tending to resist lengthening and a fall of tension in response to shortening—could always be demonstrated, and they clearly favoured the preservation of the particular length or "set" of the muscle at the commencement of stretch or of shortening. These myotatic reflexes, as Sherrington called them, were considered by him to underlie the phenomenon of muscle tone, and he suggested at the same time that the knee-jerk was but a fractional example of such reflexes—the response to a stretch of extreme brevity and slightness. These very qualities determined the character of the response evoked in that the stretch being neither extended nor maintained, the resulting contraction was only transitory. If we are to accept this conception of the tendon-jerk as a fractional example of the general response to stretch, we should be able to recognize operative in its production the same mechanism as has been discovered to subserve the myotatic reflexes as a whole.

The current conception of this mechanism has been elaborated from a study of simultaneously recorded mechanical and electrical changes in the active muscle.

Such records have been made by Fulton and Liddell [28], who find that during the course of continuously increasing stretch a series of small and irregular action currents can be detected. During the plateau of maintained tension, after further stretch has been arrested, even these disappear, and the string of the recording galvanometer remains practically stationary. If the stretch either during its progressive increase or its steady maintenance be made in any way discontinuous, e.g., from irregularity of the stretching apparatus or from shaking the table upon which the preparation is supported, there occurs a sudden well-marked electrical variation corresponding to each discontinuity. The way in which such a sudden electrical variation can most readily be produced is by tapping the stretched muscle itself or its tendon. Such an action current is seen to be followed by a short "silent period", during which both the small electrical changes, if otherwise present, and the increased tension, fall away.

Since any stimulus which normally inhibits contraction of the muscle will cause its immediate relaxation from the plateau corresponding to maintained stretch, it is clear that throughout this plateau efferent discharges must be coming into the muscle to maintain the contraction, and the most probable explanation for the fact that no current of action is detectable by the galvanometer is that they are completely asynchronous and never attain a measure of simultaneity sufficient to register electrically by summation of effects. It is assumed that these efferent excitations are sent down in response to a stream of impulses afferent from the muscle nerve-endings sensitive to stretch. The stretch being continuous, the afferent disturbances are uniformly spread out.

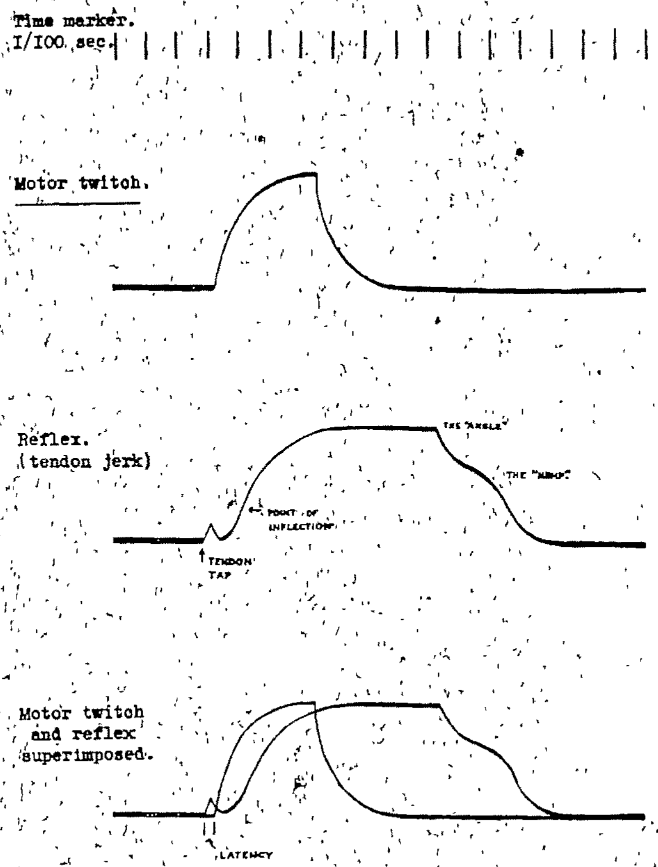


FIG. 2.—A diagram illustrating the differences between the knee-jerk and motor twitch records obtained from the cat. (After Balliff, Fulton and Liddell, with permission.)

It is clear that, if this be so, then any sudden increase of stretch will initiate in these end-organs a volley of afferent impulses, whose volume and simultaneity will be directly proportionate to the brevity and extent of this sudden stretch, so that the tap to the muscle or to its tendon, as above described, will be the most favourable way of producing a large, nearly simultaneous volley of impulses, which return to the muscle via the central nervous system, as efferent disturbances, and there sum both temporally and electrically into one longer current of action. It was found by measurement that the resulting electrical variation occurred in the quadriceps femoris muscle of a rabbit from 6 to 8 after the discontinuity of stretch by which it was initiated.

It has already been pointed out that the adaptation of tension in the muscle to its length at any given moment is present under even slight degrees of passive extension. The sudden increase of stretch caused by tapping the tendon of a muscle under such slight passive extension—i.e., the tendon-jerk of the muscle—giving rise to a reflex contraction associated with a well-marked brief action current followed by a period of electrical quiescence, can thus be readily explained.

If we compare the mechanical and electrical changes of the tendon-jerk with those following a single maximal break shock stimulation of the motor nerve (fig. 2), we find that they both show a gradual ascent, a plateau and a curve of relaxation preceded by an "angle," and their current of action a single, large, initial electrical disturbance. But while in general form they are very similar, there are certain constant differences. Thus in the tendon-jerk the angle of inflexion on the ascent of the curve is proportionately higher up, the maximum plateau height is less, the "angle" is less sharp, the descent is interrupted by a hump and the electrical disturbances more spread out. Most of these differences can be explained as being due to the slightly asynchronous character of the efferent volley in the case of the tendon-jerk. Thus we can see that the characteristics of the tendon response are due to a degree of simultaneity of stimulation which is completely absent in the gradual, continuous, stretch reflex, and maximal in the motor twitch.

The interruption of the descent or relaxation alone demands another explanation, and it can be shown to be associated with the "silent period" in the galvanometric record: this is due to proprioceptive inhibition arising within the muscle and set up either by the occurrence of the action current itself or of some other underlying change. It lasts for a considerable period after this electrical disturbance, and its cessation coincides with the hump upon the curve of mechanical relaxation.

A more detailed consideration of the variations in the operation of the whole mechanism will be deferred until the subject of clonus is dealt with.

There is some evidence [Fulton and Liddell] for the belief that it is the Golgi tendon-organ which is sensitive to stretch, and initiates those afferent disturbances which, summing up the origin of the motor units, give rise to the efferent impulse. Since the facility of this reflex varies considerably under different conditions, it has been assumed that these efferent stimuli sum centrally not only with one another, but with a variety of other influences, some tending towards facilitation, others towards inhibition, of the reflex. Many allied phenomena can be best explained upon the assumption that adequate excitation of the motor unit involves summation up to and above a certain threshold, and inhibition the removal of the accumulated central disturbance, whatever its nature may be. On the cessation of inhibition there will be many central junctions at approximately the same degree of summation, and also, since there is a temporary acceleration of the rate of discharge following inhibition, the chances of temporal overlap of impulses will be greater. It follows from this that the synchronous stimulation of many motor units will not only be forwarded by the synchronous arrival of efferent impulses, but will also tend to occur after inhibition. This synchronizing effect of inhibition is seen in the production both of the hump upon the descent curve of the tendon-jerk with the increased action currents which accompany it, and of clonus. The latter, occurring under suitable conditions of central excitability, may thus be regarded (Denny Brown [151]) as a series of rebounds from inhibition. This inhibition in the case of the stretch reflex we have seen above to be of proprioceptive origin, and there is good reason (Denny Brown) to suppose that the muscle spindles are the receptor organs that initiate it.

That the stretch reflex can be obtained with greater facility from some muscles than from others appears to be due to modifications not only of the conditions of summation and facilitation at the central nervous connections, but also of the purely peripheral mechanism. The distribution and threshold of the end-organs varies from muscle to muscle as does also the character of the muscle fibre itself. Thus the limb extensors, or antigravity muscles, show a much greater readiness of response than do the flexors, and within any one group, or indeed with any one muscle where this is composite in structure, we find that there is a constantly lower threshold to stretch stimulation shown by the slow, red series of muscle fibres than by the pale, quick series. The result of this differentiation is that when the total exciting agent—i.e., stretch afferent impulses summated with central excitability—is low, the red slow muscles respond alone, and as this agent increases with increase of either of its components, proportionately more and more of the pale muscle fibres become thrown into action and the response changes correspondingly in form, with increase both of rapidity and height of contraction.

These changes are most clearly to be observed when the conditions of peripheral stimulation remain constant and the central excitability is varied. Thus it is found that the spatial orientation of the labyrinths exercises an influence upon the magnitude and facility of the stretch reflex; there is a position in which their influence is maximal and another in which it is minimal; associated with the maximal position, which presumably increases the central excitability of the reflex, we obtain a higher degree of tension development, which both falls and rises more abruptly, the reverse holding good for the minimal position. Exactly the same forms of influence result from the operation of other means of raising and lowering the central excitability—the tonic neck reflexes and cortical or mesencephalic factors.

Regarding the knee-jerk as a fractional form of stretch reflex to the vasto-crureus one would expect the above conditions to be similarly operative in determining its facility and form, and such indeed appears to be the case. These modifying influences and their results have been examined in greater detail earlier in this paper and it must suffice here to mention that the generalizations above made for their behaviour in respect of the stretch reflex obtain also for the tendon-jerk. An increase of central excitability, whether from an increase of the peripheral stimulus or of the adjuvant central nervous factors, leads to a spread of the response to include units of higher threshold. The vasto-crureus, with which we are dealing, being a muscle which in respect of its fibres shows a compositely graded structure with red slow elements and pale quick elements, the progressive spread of the response with increased excitation leads to easily recognizable modifications in the shape of the mechanical contraction and its associated electrical variations. With minimal central excitability the slow units of low threshold are activated by the knee-jerk, giving a curve of long duration and small tension development—when maximal the curve takes the form of a higher, shorter jerk.

These changes follow alterations in labyrinth orientation and mesencephalic influence and are conspicuous in the difference between the spinal and decerebrate knee-jerks. When the spinal centres are isolated by functional interruption of the cord proximal to them, the lowering of central excitability leads to restriction of the response to the units of comparatively lower threshold, the jerk being essentially of the low protracted type and the reflex to slow stretch minimal in extent and facility. During the recovery from shock which follows acute interruption of the cord, the tendon-jerk can be elicited for some considerable period before slower stretches become again operative. This differentiation may be explained as being due either to increased potency of synchronism of afferent stimulation when the central excitability is low, or to the fact that with minimally developed stretch response the muscles are almost completely slack and extended so that the endomysium exerts a splinting action upon the muscle fibres and opposes to any attempt at stretch an elastic resistance which prevents stimulation of the muscle-stretch afferents unless the stretch is particularly rapid and extensive.

The converse of this picture is also true. Just as a raising of central excitability by optimum condition of the adjuvant factors—labyrinth neck and mesencephalic influences, etc.—facilitates and increases the response to slow stretch, so the presence of a background of a highly developed stretch reflex is associated with well developed, facile tendon responses. This accounts for the well recognized association between the tendon-jerks and the degree of muscle tonus and is seen with particular clearness in the case of flexor muscles. Here stimulation (e.g., to an ipsilateral afferent nerve) which when maximal causes a flexion reflex, when minimal leads to much increased facility and extent of the tendon responses in the same muscles. The observation that when passive stretch is very extensive or spasticity of the limb very great no detectable additional shortening follows a further sudden increase of tension provided by a blow on the tendon, is not inconsistent with this view. If the current of action in the muscle is taken as an indication of response it is found, even when the stretch reflex is already so much in operation—i.e., the reflex tension is so high, that the blow is followed by no further increase in tension—that there invariably ensues with the usual latency after each blow a large action current and succeeding silent period. This shows that the added sudden stretch has provided that transitory synchronism and resultant proprioceptive inhibition which is the distinguishing feature of the tendon-jerk.

These considerations lead to the conclusion that the characteristics of a tendon response, e.g., of the knee-jerk, strongly support the view that this is a true reflex contraction. It provides, of the myotatic or stretch reflexes, one example whose essential peculiarity follows from the synchronism of afferent excitation and motor innervation, and it stands in sharp contrast to those steadily maintained contractions which are normally provided by complete asynchronism of the activating impulses.

APPENDIX II.

THE LATENT PERIOD.

This time may be considered to be the sum of the following elements: the latent period of the receptors in the muscle, the time taken in conduction to and from the spinal cord, that necessary for linking up the afferent and efferent paths within the central nervous system, and finally the latent period of the muscles to direct stimulation. The time-interval between the entry of the disturbance into the cord and its emergence, called the "true" or "reduced" reflex time, since it is so much greater than would be required for the conduction of the disturbance along a nerve whose lengths were equal to the thickness of the cord, must be due to the discontinuity of the path within the cord and counted as delay at one or more "synapses" required by the intercalation of intraspinal neurones. By far the largest element of those contributing to the total latency of the knee-jerk is that due to peripheral nerve conduction, and if we are to make any valid deduction from experimentally ascertained values, as to the reduced reflex time ("synapse" time), it is clear that we must discover some reliable value for the velocity of the disturbance in these nerves. Piper's original measurement was 123 m./sec. for human myelinated nerve, but this is generally agreed to be too high a value, and most other workers give results which range around 65 m./sec. (Munniel [58], Helmholtz [33], Alevek, Schaffer). In a man of average stature the nervous pathways to and from the cord had a length of about 120 cm., and the time taken for the disturbance to travel this distance will be 0·018 sec. In Snyder's [82] analysis of his results he gives the following estimated values:—

Nerve conduction	10
Synapse time	3
Receptor and effector latency	3·6
Total latency.. ..	16·6

and explains the discrepancy between this figure and his observed value for the latent period (11·3) as being due to modifications introduced by unassessed factors. It is clear that here he has taken the higher figure of Piper, 120 m./sec., for the velocity of the disturbance in nerve, giving a nerve time of about half the above estimated value. The latency of effectors and receptor is generally accepted to be in the neighbourhood of 3 σ (3·6 σ is the figure taken by Snyder).

The synapse time for other reflexes cannot be given as a value whose estimation is independent of the above measurements, as it has invariably been estimated from experiments which have involved nerve conduction and hence the values obtained are dependent upon the assumed rate of conduction in nerves. For similar reflexes widely differing values have been obtained, e.g., for the masseteric reflex 1σ (P. Hoffmann [36]), and 2 σ (Jolly [45]), and for the Achilles reflex 8 σ (F. A. Hoffmann [35]).

Taking as correct in each case the smallest values which have been suggested as the result of properly controlled experiments, we see that for the knee-kerk to be reflex in nature appears to demand an interval of $3 + 1 + 10 = 14$ σ between the stimulus and the response.

COMPARISONS BETWEEN LATENT PERIODS OF KNEE-JERKS WITH THAT OF THE CONTRACTION IN RESPONSE TO OTHER FORMS OF STIMULI.

The contraction of the quadriceps femoris which has been held to follow mechanical stimulation whether directly of the muscle (Reinhard [69]), or of the skin around the patella [44], have both shown a delay in onset which is very definitely greater than that of the knee-jerk.

The only other form of stimulus of which the results have been recorded and measured is electrical stimulation over the motor point of the muscle. Forster, in 1897, claimed that the latent period of this response was greater than that of the knee-jerk; Dodge [16] found the reverse from his measurements. If Snyder's value of 2·5—3·6 for the latent period of direct stimulation is reliable it is obviously very much shorter than any delay recorded or suggested for the tendon-jerk.

A COMPARISON OF THE LATENT PERIOD OF THE KNEE-JERK WITH THAT OF OTHER MUSCLE REFLEXES IN MAN AND IN ANIMALS.

One of the earliest studies of reflexes with which comparison was made was the wink reflex in response to electrical stimulation of the conjunctiva. Exner and Waller both measured this and found that the latent period was 57—66 σ and 50 σ respectively. Subtracting the conduction time and direct muscle latency from his figures, Exner concluded that the reduced reflex time lay between 47 and 55 σ. At the time when this result was published this value was smaller than the value for the latent period of the knee-jerk, but since more accurate measurement has shortened the latter figure so much it is now well above the accepted value, and falls into line with the other skin reactions in showing a delay which is characteristically big in comparison with that of the tendon phenomena.

Dodge found that the latency of the Achilles jerk was 11—18 σ greater than that of the patellar jerk, and agrees with other workers in ascribing these differences to the variations in length of the conducting paths. The same explanation is advanced by P. Hoffmann [36] to account for the shorter latent period of the knee-jerks in children (14—17 σ).

Of other animals where the knee-jerk has been measured the frog gives values of 11·4 σ (Jolly [45], and 15 σ (Dodge [16]); the rabbit 8 σ (Waller [90], and 22 σ (Scheven); and the cat 6·6 σ in spinal and 9·1 σ in decapitate preparations (Jolly [45]). The "reduced latency," i.e., synapse time, has been estimated by Jolly as being 3·7 σ for a frog and 1·8 σ for a spinal cat.

The smallness of these figures in comparison with those from man are probably due to the comparative shortness of the peripheral nervous pathways in spite of the fact that the velocity of conduction within these pathways is less. Jolly has also compared the latency of ipsilateral and cross extension reflexes and finds a difference of 1·4 σ, which he explains as due to diminished intraspinal pathway in the case of the ipsilateral response.

The other muscle-stretch reflexes the latency of which may be compared with that of the knee-jerk, are those from the masseter given by P. Hoffmann as 7 σ and from the Achilles tendon 22—44 σ (F. A. Hoffmann).

APPENDIX III.

THE TENDON-JERK AND OTHER MUSCLE RESPONSES.

Since contractions may be observed in most muscles to follow direct percussion over the main contracting mass, a comparison of such responses with the phenomena with which we are properly dealing may be expected to throw light upon the reflex or local nature of these last. Reinhard in 1884 published [69] some observations upon this subject in which he came to the following conclusions:—

The tendon-jerk is most often a contraction of the whole muscle—referred to as the "total" response; that which follows local percussion is often a partial swelling limited to the neighbourhood of the blow—the "local" response.

The local response requires a stronger stimulus and varies considerably with its magnitude; the total contraction more rapidly reaches a maximum with increase of the stimulus and may then irradiate to other muscles.

In distinction, the local response persists during physiological sleep and that due to narcotics; in the latter condition less stimulus is required to elicit it.

In post-epileptic states the total contraction becomes harder to elicit or disappears; the local response remains unaffected.

Whereas in spastic limbs the local response is hardly visible and the total contraction much exaggerated, the reverse obtains in some flaccid cases as in tabes dorsalis.

In the early stage of atrophic paralysis the total contraction alone is often increased in facility; later it becomes much diminished, and the local response subject to much increase with changes in the electrical reactions. After death the total contraction begins to show diminution in one minute, and usually does not survive forty to sixty minutes; the local response is more facile in the first two hours, and does not disappear usually under five to six hours.

That the local effect is peripheral, direct muscular response is shown by its survival after curare.

Salomonson [94], working with a string galvanometer, has by this means divided muscular contraction into three groups:—

(1) Simple twitches preceded by a single action current.

(2) Those showing an irregularly alternating current of action.

(3) Those with no current of action.

The tendon responses he finds come into the first group; voluntary movements, epileptic and myoclonic convulsions into the second; muscle spasms, as in spasticity, tetanus and veratrine poisoning into the third.

Both of these workers, therefore, produce evidence to suggest that the tendon reflexes are essentially different from muscular contractions known to have a purely local origin.

APPENDIX IV.

A Discussion of Available Methods of Study.

When a muscle is thrown into increased activity it tends to contract. The mechanical changes which this entails are an approximation of its two ends and a thickening of its crossed section. Associated with the tendency to shorten is the development of tension, and with the tendency to thicken is an increase in the hardness or resistance to compression. Any of these quantities may be recorded separately but not entirely independently. Changes in length and tension development may be produced and measured with a considerable degree of mutual independence and approximation to isotonic and isometric records.

It is more difficult to separate changes in thickness and resistance to compression; changes in length of the muscle have previously always been recorded as secondary changes produced in the relative disposition of the limb segments to which the muscle is attached and which are moved when it contracts. Changes in its thickness have been recorded as the movements produced in some rigid lever pressed against the body of the muscle and raised as the cross section and resistance to compression—i.e., its " hardness,"—increased.

The complex structure of the muscles used and their disposition in the body allow of no accurate correlation between thickening and shortening records either in their general form or in their time relations. In those obtained by leading from some segment of the limb acted upon by the contracting muscle the additional factors introduced by the inertia and momentum of the part moved, the unknown participation of the other muscles acting upon the same part, especially of the physiological antagonists, and the necessity for the conversion of an angular into a linear movement, are all difficulties which prevent the resulting curves from being comparable with the direct shortening curves of detached muscle.

" SHORTENING " METHOD.

No record of the shortening of the muscle has been made apart from the movements of the leg thereby produced, and it is obvious that the presence of the attached passive mass of bone and soft tissues must profoundly modify the course of the contraction. Its moment of inertia will retard the onset of shortening and increase the apparent latent period—during the active contractions it will cause a lag proportional to its mass and correspondingly great because of the high mechanical disadvantage at which the muscle acts: the cessation of contraction and onset of relaxation will be altogether masked by the angular momentum of the parts and their final arrest under gravity or other restoring forces tending towards the original position of resting equilibrium. Many attempts have been made to minimize these effects. Thus Bowditch and Warren had their subject lying upon his side with the whole leg supported by a series of trapezes so that it moved entirely in a horizontal plane: a position which did not alter in any way the distorting effect of the inertia of the system moved, but lessened the effect of gravity.

There have been very many records taken by means of a string or wire, etc., attached to the foot. Bechterew used a rigid lever hinged to an anklet clasped about the leg and resting at its other end against a tambour. Tuttle, as late as 1924 [87], used a wire from the heel; Lombard [48] recorded the excursion of the foot in a similar manner, and also made use of a long lever fixed to the skin over the patella which moved with the tilting of this bone as the knee became further extended. In order to get some value for the latent period, most observers have employed a delicate electrical contact so placed, e.g., behind the heel, that it is broken immediately the knee begins to extend. The result of such observations has been to provide a number of comparable values for the latent period but no comparable records of the course of the contraction. It should be noted that whether records are taken from the foot, the leg, the patella or the belly of the muscle, so long as contraction entails a displacement from rest of the lower leg the records will be subject to the distortion outlined above—delayed by inertia at their commencement and prolonged by pendular overthrow before their cessation.

"THICKENING" METHOD.

The thickening of the muscle on contraction has been recorded in various ways. Dodge [16] recorded the movements of a spring pressed lightly against the skin over the thigh. Purves Stewart [68] employed the breaking of a circuit in which were included aluminium rods fixed to the skin and tilting with deformity due to swelling of the muscle. Sternberg [83] used a tambour fixed round the thigh with pneumatic connections to a stylus. Rosenhein strapped on to the surface of the skin over the quadriceps a piece of apparatus containing a two-point electrical contact which was broken by stretching of the strap against an adjustable spring when the muscle swelled. Many observers such as ter Meulen [85], Jarisch and Schiff [42] and others as early as Brissaud [13], used these and differing pieces of apparatus for recording the same change.

It is clear that the results of such experiments cannot be compared with those of other methods, or even *inter se*, except in respect of the latent period, and even here the correspondence cannot be expected to be very exact. If one could reasonably assume that the whole thigh is deformed simultaneously and proportionally with the change in thickness of the underlying muscle; that the shortening marches *pari passu* with the thickening or even commences at the same instant; that the whole muscle thickened simultaneously and to a proportionate degree throughout its length, then a greater degree of correspondence might be anticipated. Of all these unjustifiable assumptions the least unjustifiable is that which supposes a simultaneous commencement of shortening and thickening—to this extent then values obtained for the latent period may be compared with those obtained from shortening experiments.

Another discrepancy arises from the fact that when stimulated the muscle may harden or change its cross-section shape without any decrease in length. Since no shortening can occur until the inertia of the parts to which the ends of the muscle are attached is overcome, the latent period of hardening would be expected to be less than that of shortening, and this is generally the case.

To note the sequence in which thickening appears at a number of arbitrarily selected points on the thigh and to deduce from this sequence the course of the wave of excitation which must have passed among the muscle fibres beneath these points, can have no validity.

A study of the physical factors involved shows that there can be no correspondence expected between the time relations of shortening and of proportionate degrees of thickening, for, considering the muscle to be a roughly ellipsoidal shaped mass of constant volume and the whole of its substance to be equally contractile, we see that the relation between changes in the longitudinal and any transverse diameter invoked by a change in shape of the muscle in the direction of a more spherical form is given by $4/3.\pi x^2 y = k$, when x = maximum cross-section diameter, y = longitudinal diameter, k = some constant, i.e., $y = 3k/4\pi x^2$, or $dy/dx = -3k/2\pi x^3$, so that as x, the thickness, increases, the rate of decrease of y, the length, falls off considerably. Hence the relation between the shortening and the thickening varies considerably, and the shortening per unit increase of thickness decreases rapidly as the muscle becomes thicker.

Finally it must be allowed that shortening and lengthening are the changes whereby the muscle functions in the body, while thickening and hardening are concomitant changes which are determined secondarily by purely physical conditions. Each muscle is designed so that it can most advantageously pull upon its tendon when its component fibres shorten, and in measuring shortening we are measuring the essential change to which all parts of the muscle contribute proportionately. In recording thickening we are sampling some arbitrary cross-section across which the various muscle fibres will probably be contributing very differently to all but maximal thickening effects, and such maximal thickening we know never occurs in reflex contractions.

APPENDIX V.

MEASUREMENT OF THE CURVES.

Some of the records here included were obtained by leading a string direct from the patellar support, round a pulley and on to a stylus which scribed against a moving smoked surface. This method was discarded as soon as it became obvious that the distortions introduced by this apparatus obscured the essential characters of the curve of contraction. Some of the results so obtained are, however, given below, as the record could be run for a much longer time than was possible with a photographic plate falling at the same speed. Some effects, and notably that of continued clonus, were more easily demonstrated in this way.

CURVES OBTAINED WITH GRAPHICAL RECORDING.

The only features of these curves which reproduced the undistorted contraction of the muscle with sufficient fidelity to justify their measurement were the relative height of successive responses and the rate of clonus when this occurred.

The normal curve obtained had the general form here reproduced, and the points from which measurement was made are indicated upon the diagram (fig. 3).

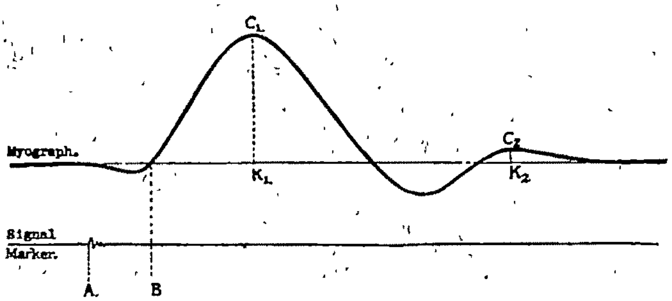


FIG. 3.—A diagram of the normal knee-jerk as obtained with the graphic method of recording, indicating the points from which measurements were made. (Read from left to right.)

For continued clonus the intervals between successive contractions are K_1, K_2, K_2, K_3, K_3, K_4, etc. Some of the curves at the end of this paper are reproduced as tracings from the varnished smoked-paper records, others as photographs of these records themselves.

CURVES OBTAINED WITH PHOTOGRAPHIC RECORDING.

The general form of the curves has been previously described.

The characteristics of each curve selected for measurement were those which could be seen to vary from patient to patient, and also those which from a theoretical consideration could be expected to be of significance. The points O, X, A, B, C, D, from which measurement was made, are indicated upon the diagram (fig. 4).

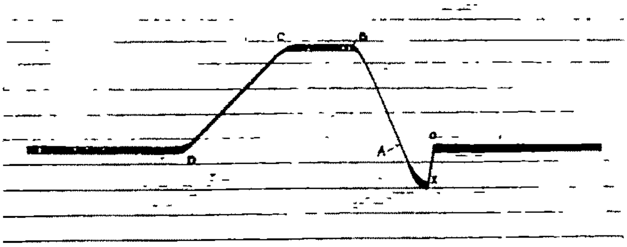


FIG. 4.—A diagram of the normal knee-jerk as obtained with the photographic method of recording, indicating the points from which measurements were made. (Read from right to left.)

The vertical distances on the record provide a magnification of the actual distances moved through by the patella. The magnification for each record was determined by comparing the width of the bar fixed to the recording needle with that of its shadow. This ratio gave a factor for the reduction of all vertical distances on the plate into corresponding distances at the patella.

Horizontal distances were reduced to time intervals by comparison with the shadow cast by a tuning-fork vibrating 100 times per second. Since it could not be assumed that the plate fell in the camera with uniform speed, each distance had to be compared with the time-marker shadows immediately beneath it. This was done by using a double-microscope comparimeter with which to compare selected points on the curve with others on a fixed millimetre scale. Every fifth indentation of the time-marker shadow was then similarly given values from the same scale and the requisite intervals evaluated.

THE LATENT PERIOD.

The moment of incidence of the blow upon the patella was not measured by the making of an electrical circuit in most of the records, because this involved not only the unknown latency of the recording mechanism but also the time taken for compression of soft tissues when these necessarily intervened between the instrument and the rigid patella. It was found that the moment of stretch was so abruptly marked upon the records that its measurement to within 1 σ was reasonably accurate.

The selection upon the records of the moment of commencement of reflex muscular contraction presented the greatest difficulty in the estimation of this quantity—the latent period.

The instrument adjusted in position upon the patient's leg presented the condition of two elastic bodies in equilibrium, the stretched muscle and the extending spring. In the absence of any additional forces applied to this system, e.g., that supplied by the physiological response investigated, the displacement of the point of application of these two opposing forces in the direction of the spring should lead, when released, to a damped oscillation of the system about the point of equilibrium. The only really satisfactory means of determining the moment of entry into this field of the additional force—that supplied by the reflex muscular contraction—is to obtain records from this system both with and without the reflex present, and after superimposition of these two records to determine the point at which one departs from the other—this point can then be taken as indicating the moment at which the muscle contraction commenced.

In practice this can only rarely be done. Since with identical conditions the procedure employed either does or does not give rise to contraction of the quadriceps, it follows that two such curves cannot ever be obtained. On those occasions on which, without altering any of the conditions under control, identical stimuli gave at one time no response, and, on repetition, a definite contraction—and these were not rare, but occurred quite fortuitously—the immediately obvious assumption had to be made that one of the many uncontrollable factors: attention, internal inhibition or facilitation, changes in tonic innervation, etc., had become altered.

The alternative was to obtain a series of records under conditions of variation of one controllable factor, e.g., by using various grades of initial tension designedly insufficient for the eliciting of a reflex, and then by extrapolation of the results obtained, where consistency justified this, to deduce a theoretical "base line" upon which to apply the curve obtained after the tension had been raised sufficiently for the muscle response to appear. The results obtained from measurement of the curves, taking at the moment of onset of the muscular contraction a point of obvious discontinuity in what should be a smoother curve—

where this point was not otherwise explainable—have yielded fairly constant results, and results in accord with those obtained by other observers in this field, as far as the normal response is concerned.

The horizontal distance between O and X, where O is the moment of onset of stretch-stimuli and X the moment of discontinuity as above defined, has to be compared with the distance between the underlying time-marker shadows. If this distance be O X, and D the distance between the first and last of the ten time-intervals recorded immediately below, then the latent period is $= \frac{OX \, . \, 100}{D} \sigma$.

THE SLOPE OF THE ASCENT.

The curve of ascent was in all normal cases rectilinear for the greater part of its extent. Its lowest part was concave upwards as contraction commenced, and it was slightly rounded off at the top where it merged with the plateau. It would have been a convenience had these departures from the linear form been sufficiently small to be neglected, and the highest point B sufficiently well defined so that the co-ordinates of points required for other measurements could be used also in this determination. Unfortunately this was rarely so, and in all cases the slope of the rising phase was determined by measuring the co-ordinates of two points as far apart as possible upon the perfectly rectilinear part of this curve. These figures were used, by reduction of the magnification and comparison with the time marked, to find the slope in terms of millimetres displacement of the patella per sigma interval of time.

The height of the contraction was taken as the ordinate distance between A and B where A was the point at which the rising curve cut the base-line and B the highest point attained by that rise. It is given after reduction of the magnification in terms of millimetres displacement of the patella.

The duration of the plateau in sigma intervals was obtained from the horizontal distance from B to C; C being the point of greatest discontinuity as the plateau merged into the curve of relaxation. In most normal cases, C was quite a sharp definite point on the curve, and determined with greater ease than when the descent was delayed by the addition of a hump or preliminary convexity upwards.

The total duration of the response was taken arbitrarily at the time interval (in sigma) between A and C. In physiological records the beginning of this period is generally measured from the commencement of the electrical response. It was felt that since such electrical records were not here available it was better to measure from A rather than from O or X. This avoided including in the duration time the latent period and provided two easily defined points from which to measure time intervals which were comparable for the different curves but not equivalent to the "duration of the response" as usually defined.

The slope of the fall.—In normal cases the curve of relaxation commenced abruptly at a well-defined angle and was thereafter linear or concave upwards. The only way in which the characteristic angle of slope could be determined in each case was, as in the ascent, to take two arbitrary points as far apart as possible on the strictly rectilinear part of the curve and by the appropriate magnification-reduction and time-marker comparison of their co-ordinates, to arrive at a value for the slope in terms of millimetre displacements of the patella per (sigma) unit of time.

EXAMPLES OF RECORDED RESPONSES.

1.	Normal knee-jerks	Figs. 5-8
2.	Hypertonic knee-jerks from spastic patients	Figs. 9-14
3.	The clonic knee-jerk from spastic patients	Figs. 15-20
4.	Hypotonic knee-jerks from patients with cerebellar disease	Figs. 21-22
5.	The knee-jerk in extrapyramidal (Parkinsonian) rigidity ..	Figs. 23-25
6.	The knee-jerk in chorea—the sustained knee-jerk	Figs. 26-27
7.	Illustrations of the effect of reinforcement efforts	Figs. 28-29

The myograph records (white on black) are to be read from left to right, the optically recorded curves (black on white) from right to left.

FIGS. 5-7.—Responses from healthy subjects.

FIG. 5.—Initial tension 400 gm. Time marker (above) 1/5 sec.
Signal (below) stimulus.

FIG. 6.—Initial tension 600 gm. Time marker below 1/100 sec.

FIG. 7.—Initial tension 400 gm. ,, ,, ,, 1/100 sec.

FIG. 8.—A series of responses from a normal, healthy person. The curves have been traced one above the other so that the moments of stimulation lie along the same ordinate.

The six lines below are marked each in intervals corresponding to 1/5 sec., and are numbered in accordance with the curves to which they apply.

The initial tension was the same in each case.

The distortion of the spring hammer before release was increased progressively from below upwards; the figures in brackets are proportional to the degree of distortion in each case.

N.B.—These curves illustrate the observation that with increasing strength of the blow given at this constant initial tension the height of the curve of contraction is also increased.

FIGS. 9-14.—Responses from patients with clinical spasticity.

Time marker 1/100 sec.

These curves are typical of those obtained from persons with pyramidal tract lesions. The ascent is usually abrupt, the plateau well marked, the angle obscured by the upward convexity of the first part of the descent upon relaxation and the later parts of the descent are prolonged or interrupted by secondary contractions of varying force.

FIG. 9.—G. J. A case of disseminated sclerosis. Spastic paraplegia well marked. Initial tension 300 gm. Descent almost complete, slight clonic contraction.

FIG 10.—B B. Hemiplegia. Considerable spasticity of left leg. Left leg recording. Initial tension 700 gm. Descent interrupted by secondary contraction.

FIG. 11.—A H. A patient with spinal tumour. Great spasticity of both legs. Initial tension 150 gm. The curve of relaxation shows a well marked preliminary hump with later secondary contractions.

FIG. 12.—W. P. Cerebral syphilis. Spasticity of the legs with ankle clonus. Initial tension 200 gm. Convex descent and secondary contraction.

FIG 13.—C. C. Left hemiplegia. Spasticity of left limbs. Left leg recording. Initial tension 300 gm. Time marker not included. A secondary contraction delays the later part of the descent.

FIG, 14.—The same patient as in fig. 13. Initial tension 500 gm.

FIGS. 15-20.—Responses from spastic patients illustrating the development of clonus with increasing initial tension.

Figs. 16-20 were taken from the patient J. D. who then showed well-marked spastic paraplegia and from whom a spinal tumour in the upper dorsal region was later removed.

FIG. 15.—W. B. Spinal tumour. Spastic paraplegia.
Time marker below in 1/5 sec., separate for each curve. The fraction in small figures at the beginning of each record indicates by its denominator the force of the blow and by its numerator the initial tension. From these it will be seen that the blow remained constant throughout while the initial tension was progressively increased, i e., 250, 300, 400, 500 gm. The moment of stimulation lies in each case vertically above the small indicator arrow. Permanent clonus was established at 500 gm. I.T.

FIG. 16.—Initial tension 150 gm.

FIG. 17.—Initial tension 300 gm.

FIG. 18.—Initial tension 500 gm.

FIG. 19.—Initial tension 600 gm.

FIG. 20.—Initial tension 600 gm. For this record the photographic plate was allowed to fall at a much lower rate than for the previous records in order that the regularity and permanence of the series of clonic beats might be demonstrated.

FIGS. 21-22 —Records illustrating the characteristics of the responses from patients with hypotonicity of the limbs, i.e., the sigmoid character of the curves of contraction and relaxation, the absence of any true plateau, the rounding-off of the terminal "angle," the relatively abrupt nature of the descent from the apex of contraction, and the frequency with which the curve falls, upon relaxation, slightly below the original resting base line.

FIG. 21.—D. O. Cerebellar tumour. Left side. Hypotonicity of the limb musculature suggested by ease of passive manipulation and facility of passive displacement from defective postural fixation. The hanging knee-jerk was pendular in character Left leg recording. Initial tension 400 gm.

FIG. 22.—I. A. Cerebellar tumour. Hypotonicity with pendular knee-jerks. Right leg recording. Initial tension 150 gm.

FIGS. 23-25.—Records illustrating the characteristics of responses obtained from patients with extra-pyramidal (Parkinsonian) rigidity, i e., the rounding-off of the plateau, the absence of the "angle," the relatively slow relaxation, the long delay shown in the return of the base-line to the original resting level.

FIG. 23.—W. F. Right leg recording Initial tension 300 gm.

FIG. 24.—E. S. Right leg recording. Initial tension 300 gm.

FIG. 25.—M. C. Right leg recording. Initial tension 250 gm.

FIGS. 26-27.—Records illustrating the characteristics of the responses obtained from patients with chorea rheumatica, i.e., the hypotonic character and the sustained knee-jerk. Time marker (below) indicates 1/100 sec.

FIG. 26.—G. N. Hypotonicity with choreic postures and movements. The knee-jerks normally obtained were sometimes sustained in character. Right leg recording. Initial tension 600 gm.

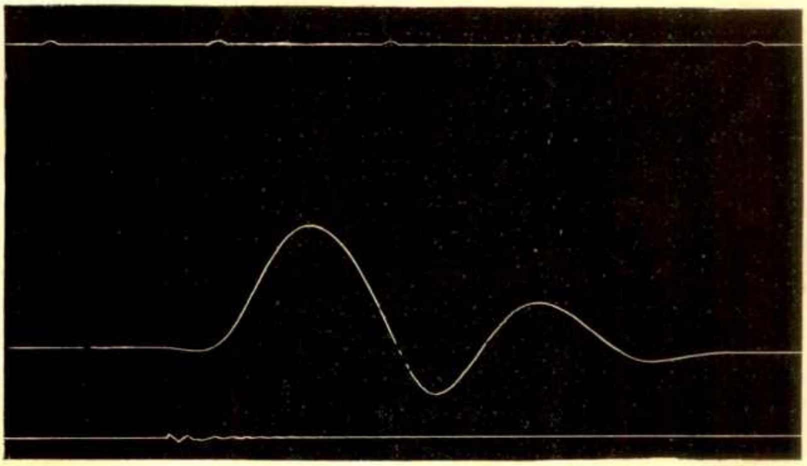


FIG. 5.

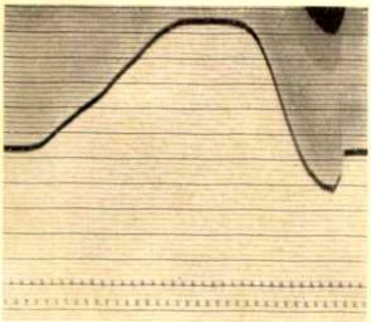


FIG. 6.

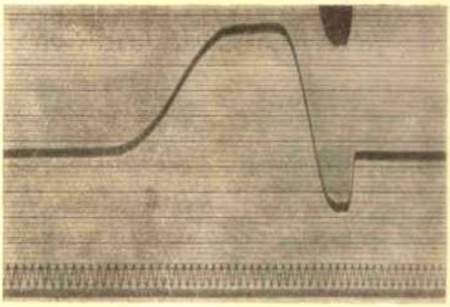


FIG. 7.

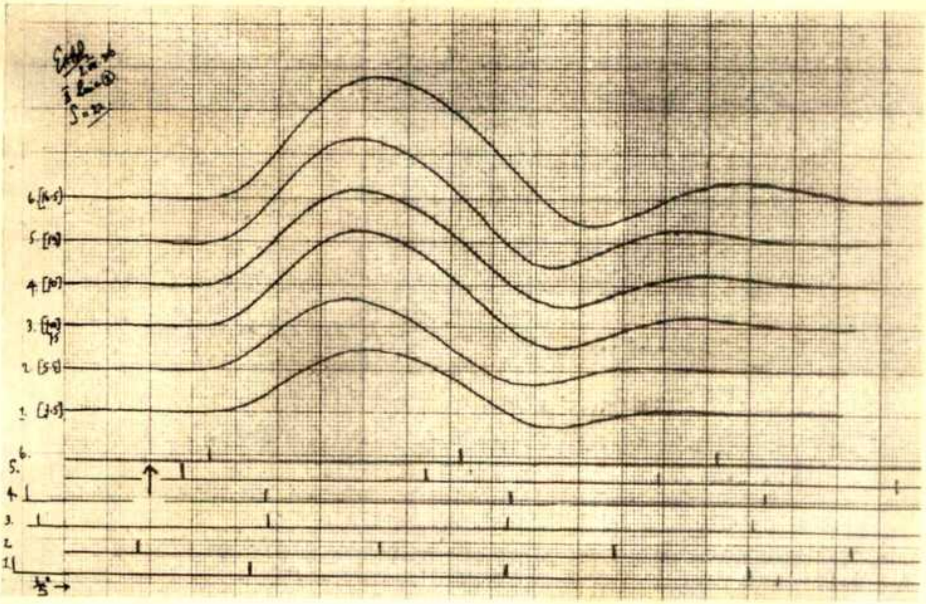


FIG. 8.

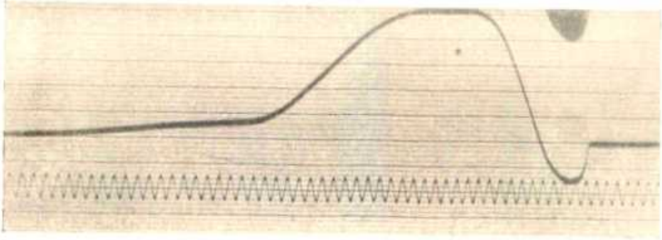


FIG. 9.

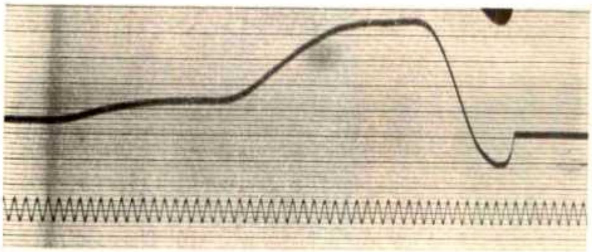


FIG. 10.

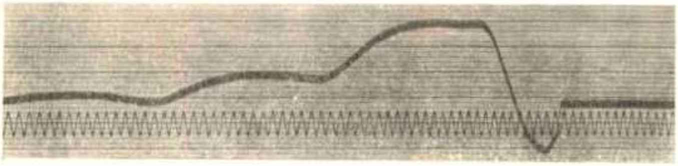


FIG. 11.

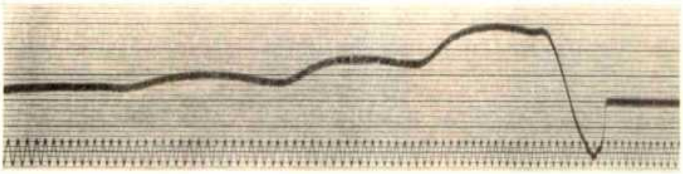


FIG. 12.

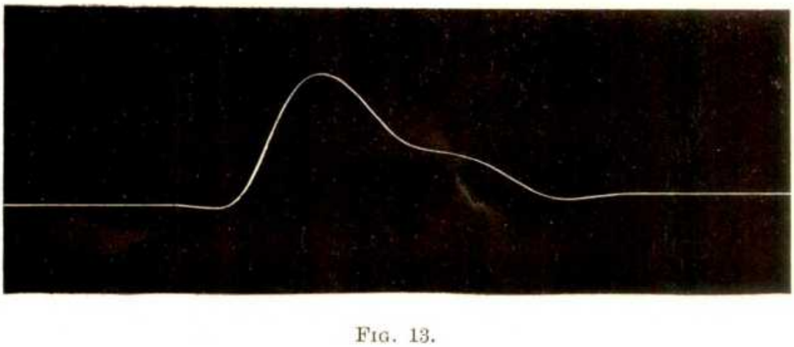


FIG. 13.

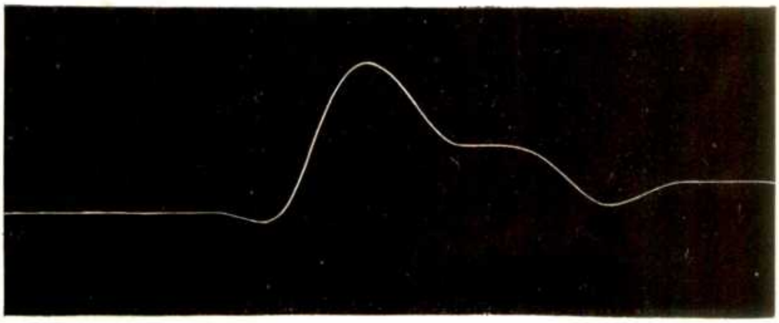


FIG. 14.

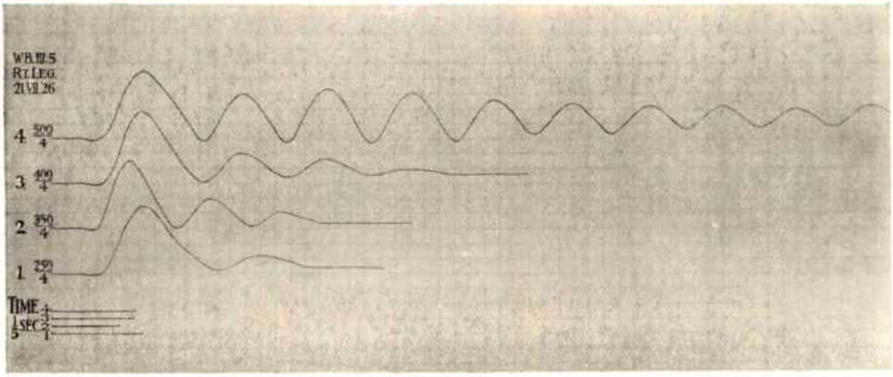


FIG. 15.

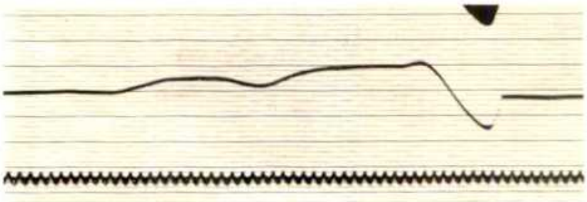


FIG. 16.

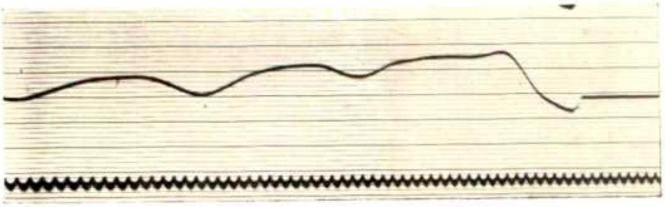


FIG. 17.

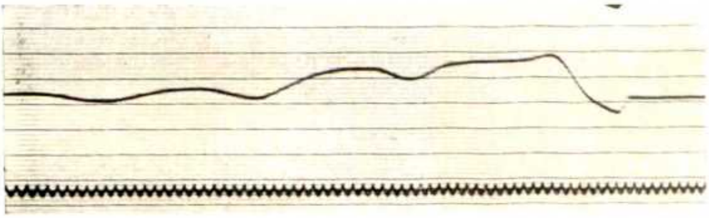


FIG. 18.

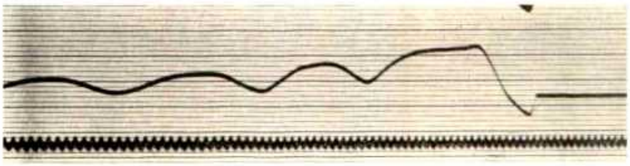


FIG. 19.

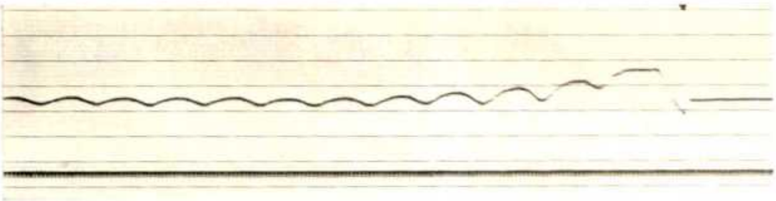


FIG. 20.

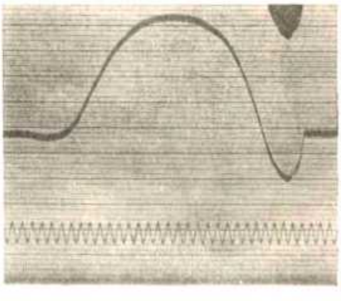


FIG. 21.

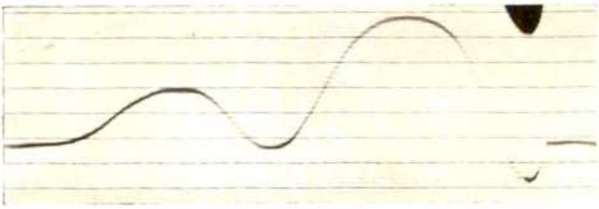


FIG. 22.

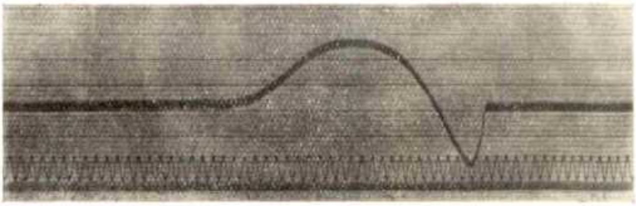


FIG. 23.

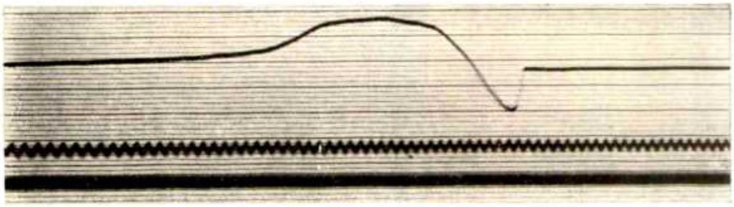


FIG. 24.

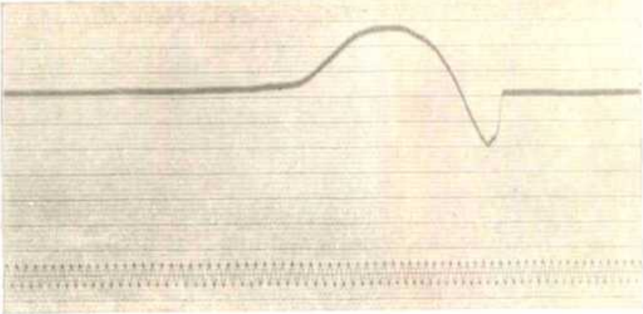


FIG. 25.

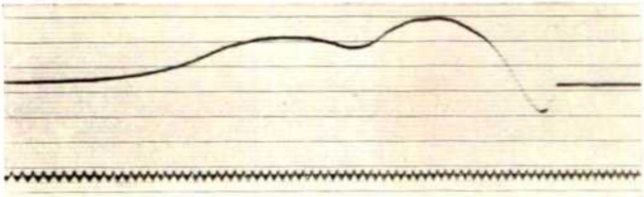


FIG. 26.

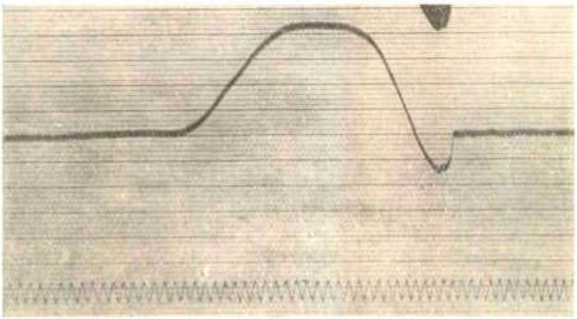


FIG. 27.

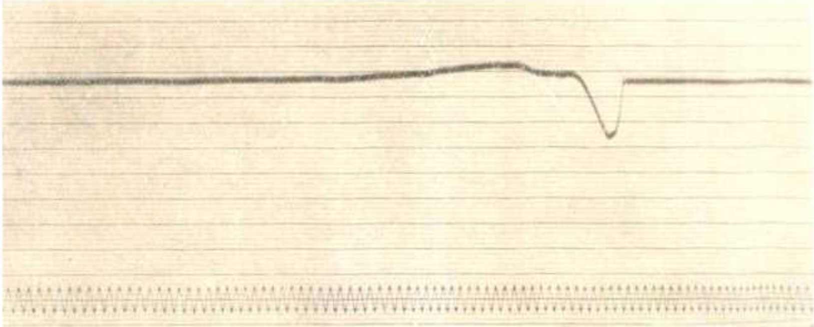


FIG. 28,

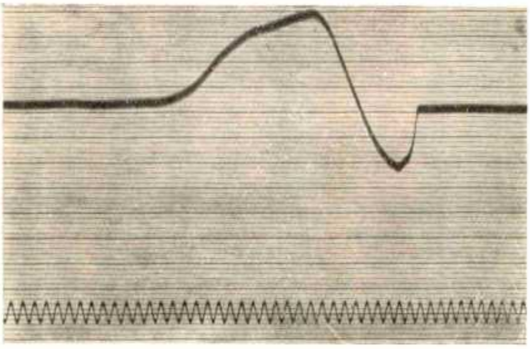


FIG. 29.

FIG. 27.—V. D. No clinical hypotonicity but some choreic movements. The knee-jerks were sometimes sustained. No records of prolonged after-contraction were obtained from this patient. Initial tension 500 gm.

FIGS. 28-29.—Records illustrating the effect of "reinforcement efforts" upon the facility of eliciting the knee-jerk. Time marker (below) indicates 1/100 sec.

FIG. 28.—A. F. Healthy person. Right leg recording. Initial tension 250 gm. Strong blow delivered. A very slight response recorded.

FIG. 29.—The same patient as in fig. 28. Initial tension 250 gm. Clenching of hands requested just before the blow was given, to be maintained during the recording. The same blow was given as in record fig. 28. A clear response of good amplitude resulted.

TABLE I.

A comparison between the minimal initial tensions required for eliciting a response from (*a*) normal } persons.
(*b*) spastic }

Patient	Condition	Minimal initial tension
I. A.	Cerebral tumour	100
J. D.	Spinal tumour	100
G. J	Disseminate sclerosis	200
W. H.	Spino-cerebellar ataxy	200
H. P.-S.	Hemiplegia	150
A. W.	Disseminate sclerosis	200
F. H.	Hemiplegia	200
P. M.	Amyotrophic lateral sclerosis	150
R. B.	Normal	400
W. B.	Neurasthenia	300
H. B.	Cervical rib	300
Z. C.	Cerebellar tumour	400
A. C.	Normal	350
W. C.	Normal	300
B. P.	Normal	350
B. R.	Normal	400
I. D.	Normal	300
F. D.	Normal	350

This shows that in spastic cases with increased facility of the response the minimal effective initial tension is lowered.

TABLE II.

Illustrating the effect of variations in (*a*) initial tension,
(*b*) force of blow,
upon the amplitude of the response.

I. T. = initial tension in grammes weight.

S. = a number obtained from the setting of the apparatus which indicates the degree of distortion of the spring-hammer before release. The numerical values of these figures is in inverse proportion to this degree of distortion, i.e., the smaller the number the greater the blow delivered.

C_1K_1 = height of the plateau in millimetres above the base line

Patient, M T. Ward I, bed 14. Spastic paraplegia.
6.vii.26. Left leg recording.

Record	I T.	S.	C_1K_1
1	150	3	7·5
2	150	5	16
3	150	7	20
4	150	10	22
5	200	7	17
6	200	7	17
7	250	3	7·5
8	250	5	14
9	250	7	17
10	300	5	12
11	300	7	15

This table shows that for this patient the amplitude of the response within this range of values is increased by increasing the force of the blow.

TABLE III.

Measurement of a series of curves.

N.B.—These values represent distances measured upon the curves in millimetres and not time intervals between the corresponding parts of the contraction recorded—the smoked surface was not in all cases travelling at the same rate. The rate of clonus was arrived at by using the last curve (12) and evaluating the distances here given in terms of time intervals by comparison with the time marker.

K_1K_2, K_2K_3, &c., refer to points upon the curve as in text figure 3.

Patient, C. B. Ward VII, bed 19. Disseminate sclerosis.
26.vii.26. Right leg recording.

Curves K K		1	2	3	4	5	6	7	8	9	10	11	12
K_1K_2	..	57	49	45	55	55	53	55	50	53	52	47	38
K_2K_3	..	—	43	41	45	44	48	44	39	40	44	38	23
K_3K_4	..	—	—	38	37	36	38	31	29	33	37	28	25
K_4K_5	..	—	—	—	—	—	35	40	37	37	38	38	25
K_5K_6	..	—	—	—	—	—	—	—	—	37	40	35	25
K_6K_7	..	—	—	—	—	—	—	—	—	40	40	30	24
K_7K_8	..	—	—	—	—	—	—	—	—	38	40	30	24
K_8K_9	..	—	—	—	—	—	—	—	—	—	40	31	24
K_9K_{10}	..	—	—	—	—	—	—	—	—	—	—	30	27
$K_{10}K_{11}$	.	—	—	—	—	—	—	—	—	—	—	29	25
$K_{11}K_{12}$	..	—	—	—	—	—	—	—	—	—	—	28	29
$K_{12}K_{13}$	..	—	—	—	—	—	—	—	—	—	—	27	25
$K_{13}K_{14}$	..	—	—	—	—	—	—	—	—	—	—	—	28
$K_{14}K_{15}$	..	—	—	—	—	—	—	—	—	—	—	—	29
$K_{15}K_{16}$	..	—	—	—	—	—	—	—	—	—	—	—	28
$K_{16}K_{17}$	..	—	—	—	—	—	—	—	—	—	—	—	27
Time marker 1/5 sec.	..	68	64	65	68	64	64	68	65	68	68	62	60

TABLE III (*continued*).

Curve		1 250	2 350	3 400	4 500
K_1K_2	..	78	57	67	67
K_2K_3	..	—	57	54	57
K_3K_4	..	—	—	55	56
K_4K_5	..	—	—	—	55
K_5K_6	..	—	—	—	53
K_6K_7	..	—	—	—	51
K_7K_8	..	—	—	—	49
K_8K_9	..	—	—	—	50
K_9K_{10}	..	—	—	—	49

TABLE III (*continued*).

Curve		1 250	2 350	3 400	4 500
Distance in 2/5 sec. : time interval K_1K_2	..	121	95·5	114 5	119·5
Time interval K_1K_2 : distance in 2/5 sec	.	0·26	0·24	0·23	0·22
Distance in 2/5 sec. : time interval K_2K_3	..	—	104	119	122
Time interval K_2K_3 : distance in 2/5 sec		—	0·22	0·18	0·185
Distance in 2/5 sec. : time interval K_3K_4	.	—	—	120 5	124
Time interval K_3K_4 . distance in 2/5 sec	..	—	—	0 18	0 18
Distance in 2/5 sec : time interval K_4K_5	..	—	—	—	124
Time interval K_4K_5 . distance in 2/5 sec.	..	—	—	—	0 18
Distance in 2/5 sec. · time interval K_5K_6	..	—	—	—	124
Time interval K_5K_6 : distance in 2/5 sec.	..	—	—	—	0·17
Distance in 2/5 sec : time interval K_6K_7	..	—	—	—	126
Time interval K_6K_7 distance in 2/5 sec.	..	—	—	—	0·16
Distance in 2/5 sec. . time interval K_7K_8	..	—	—	—	128
Time interval K_7K_8 : distance in 2/5 sec.	..	—	—	—	0·15
Distance in 2/5 sec. . time interval K_8K_9	..	—	—	—	130
Time interval K_8K_9 : distance in 2/5 sec	..	—	—	—	0·15
Distance in 2/5 sec . time interval K_9K_{10}	..	—	—	—	130
Time interval K_9K_{10} : distance in 2/5 sec.	..	—	—	—	0·15

TABLE IV.

Illustrating the effect of increase of the Initial Tension upon—
The height of the contraction,
The permanency of the clonus,
The degree of relaxation during clonus.

N.B.—I.T. = initial tension in grammes weight.
O_1K_1 = amplitude of the response in millimetres above the base line.
H = height of the partial relaxations of clonus above the original resting level.

Patient, C.B. Ward VII, bed 19. Disseminate sclerosis.
26.vii.26. Right leg recording.
Drum record.

Curve	I.T.	O_1K_1	Number of after-beats	H.
1	150	1·85	1	—
2	200	2·3	2	0·2
3	250	2·4	3	0·2
4	300	3 0	3	0·4
5	300	3·1	3	0·5
6	350	3·1	4	0·75
7	400	3·1	4	0·75
8	450	3 2	5	0·75
9	450	2·9	7	1·0
10	500	2·6	8	1·0
11	600	3·4	permanent clonus	1·75
12	625	3 6	,,	2·5

Patient, W. B. Ward III, bed 15. Right hemiplegia.
21.vii.26. Right leg recording.
Drum record.

Curve	I.T	O K	Number of after-beats	H
1	250	4·5	1	—
2	350	4·5	2	0·75
3	400	4·8	3	1·0
4	500	4·5	permanent clonus	1·5

This table illustrates the observation that with a constant blow increase of the Initial Tension—

Increases the height of the contraction,
Increases the number of clonic after-beats,
Raises the level of contraction upon which clonus is established.

REFERENCES.

[1] Adrian. *Journ. Physiol.*, 1926, **61**, 49.
[2] Babinski. "Réflexes tendineux et réflexes osseux," Paris, 1912.
[3] Ballif, Fulton and Liddell. *Proc. Roy. Soc.*, 1925, **98 B**, 592.
[4] Bastian. *Trans Med. Chir. Soc.*, 1890, **73**, 151.
[5] v. Bechterew. *Neurol. Centralbl*, 1892, **34**.
[6] Beevor. *Brain*, 1883, **5**, 56.
[7] Berger. *Centralbl. f. Nervenheilk.*, 1879, **73**.
[8] Block. *Arch. f. Psych. u. Nervenkrankh.*, 1882, **12**, 471.
[9] Bohme. "Handbuch d. normalen u. patholog. Physiol.," 1927, **10**, 980
[10] Brondgeest. *Arch. f. Anat. u. Physiol.*, 1860, 703.
[11] Bowditch and Warren. *Journ. Physiol.*, 1890, **11**, 25.
[12] Bowlby. *Lancet*, 1890, **1**, 1071.
[13] Brissaud. "Recherch. anatom. pathologique, etc.," Paris, 1880.
[14] Cooper and Adrian. *Proc. Roy. Soc.*, 1924, **96 B**, 243.

[15] Denny Brown. *Proc. Roy. Soc.*, 1928, **103 B**, ; *ibid.*, 1929, **104 B** , 85.
[16] Dodge. *Zeitschr. f. allgem. Physiol.*, 1911, **12**.
[17] Dumpert and Flick. *Journ. f. Physiol. u. Neurol* , 1922, **29**, 153.
[18] Erb. *Arch. f. Psychiatr.*, 1875, **5**, 192.
[19] Eulenberg. *Zeitschr. f. klin. Med* , 1885, **9**, 174.
[20] Exner. *Pflüger's Archiv*, 1873, **7**, 601.
[21] Fergusson. *Brit. Med. Journ.*, 1890, **1**, 541.
[22] Ferrier. *Brain*, 1882, **5**, 123.
[23] Foerster. "Handbuch d. normal. u. patholog. Physiol.," 1927.
[24] Fulton. *Proc. Roy. Soc.*, 1924, **96 B**, 475.
[25] *Idem.* *Ibid.*, 1924, **97 B**, 424.
[26] *Idem.* *Ibid.*, 1925, **98 B**, 577.
[27] *Idem.* *Amer. Journ. Physiol.*, 1925, **75**, 235.
[28] Fulton and Liddell. *Proc. Roy. Soc.*, 1925, **98 B**, 214.
[29] Golla. Croonian Lectures, *Lancet*, 1921, 115.
[30] Golla and Hettwer. *Proc. Roy. Soc.*, 1922, **94 B**, 92 ; *Brain*, 1924, **47**, 57.
[31] Gotch. *Journ. Physiol.*, 1896, **20**, 322.
[32] Gowers. *Trans. Med. Chir. Soc.*, 1879, **62**, 269.
[33] Helmholtz. *Arch. Anat. u. Physiol.*, **71**, 276.
[34] Hinsey, J. *Journ. Comp. Neurol.*, 1927, **44**, 87.
[35] Hoffmann, P. "Natur d. Sehnenreflexe," *Deutsch. Zeitschr. f. Nervenheilk.*, 1924, **8**, 269.
[36] Hoffmann, F. A. "Untersuchungen u. d. Eigenreflexe Menschmuskelen," 1922.
[37] Holmes. *Brain*, 1904, **27**, 522.
[38] Karger. "Reflex, Wille und Vorstellung," *Klin. Wochenschr.*, 1924, **3**, 2278.
[39] Horsley. *Brain*, 1883, **6**, 369.
[40] Hughlings Jackson. *Brit. Med. Journ.*, 1892, **1**, 326.
[41] James. *Edinburgh Med. Journ.*, 1880, **25**, 702.
[42] Jarisch and Schiff. *Med. Jahrbuch d. Gesellsch. d. Aerzte Wien*, 1882, 261.
[43] Jendrassik. *Neurol. Centralbl.*, 1885, 412.
[44] *Idem.* *Deutsch. Arch f. klin. Med.*, 1897, **52**, 569.
[45] Jolly. *Quart. Journ. Exper. Physiol.*, 1911, **4**, 67.
[46] Lewandowsky. "Handbuch d. Neurol." 1911, **2**, 582.
[47] Liddell and Sherrington. *Proc. Roy. Soc.*, 1924, **96 B**, 212 ; *ibid.*, 1925, **97 B**, 267.
[48] Lombard. *Journ. Physiol.*, 1889, **10**, 122.
[49] *Idem.* *Amer. Journ. Psych.*, 1888, **1**, 8.
[50] Lucas, K. *Journ. Physiol.*, 1909, **38**, 113.
[51] Mann u. Schleier. *Zeitsch. f. d. ges. Neurol. u. Psychiat.*, 1924, **91**, 551.
[52] Magnus and Liljestrand. *Pfluger's Archiv*, 1919, **176**, 168.
[53] Marinian. *Rivista Clinica*, Bologna, 1884, **3**, 415.
[54] Marshall Hall. "The Nervous System," 1840.
[55] Mitchell and Lewis. *Phil. Med. News*, February 13, 1886, 20.
[56] Mommsen. *Virchow's Archiv*, 1885, **101**, 22.
[57] Muller. "Handbuch d. Physiolog.," 1884, 1, 4.
[59] Neuhof. *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1912, **13**, 444.
[60] Nonne. *Deutsch. Zeitschr. f. Nervenheilk.*, 1903, **24**, 474.
[61] Oeconomakis. *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, 1911, **6**, 85.
[62] Petitclerc. "Réflexes tendineux," *Thèse de Paris*, 1880.
[63] Pelizaeus. *Neurol. Centralbl.*, 1886, **5**, 50.
[64] Pfahl. *Zeitschr. f. d. ges. Neurol. u Psychiatr.*, 1910, **1**, 350.
[65] Piperm. *Pfluger's Archiv*, 1908, **124**, 191.
[66] Prevost and Waller, *Revue méd. de la Suisse Romande*, 1881, **1**, 613.
[67] Pritchard, B. *Pflüger's Archiv*, 1926, **214**, 148 : *Journ. Physiol.* (awaiting publication).
[68] Purves Stewart. *Journ. Physiol.*, 1897, **22**, 61.
[69] Reinhard. *Arch. f. Psychiat.*, 1884, **15**, 681.

[70] Risien Russell. *Proc. Roy. Soc.*, 1893, **53 B**, 480

[71] Rollet. *Sitzungsberichte der Kais. Akad. d. Wissensch. Wien*, 1876, **73**, 34.

[72] Rosenheim. *Arch f. Psychiat. u Nervenkr.*, 1884, **151**, 184.

[73] Sachs. *Arch. f. Anat. u. Physiol*, 1875, 802.

[74] Scheven. *Pfluger's Archiv*, 1907, **11**, 7, 108.

[75] Sherrington. *Proc. Roy. Soc.*, 1892, **52 B**, 556.

[76] *Idem. Ibid.*, 1925, **97 B**, 519,

[77] *Idem. Journ. Physiol.*, 1910, **40**, 28.

[79] Schenk u. Wissemann. *Med. Klinik*, November 17, 1927.

[80] Strumpell. "Zur Kentniss der Sehnenreflexe," *Deutsch. Arch. Klin. Med.*, 1879, **24**, 125.

[81] Schultze. *Deutsch med Woch.*, 1889, **15**, 287.

[82] Snyder. *Amer. Journ. Physiol.*, 1910, **26**, 475.

[83] Sternberg. *Die Sehnenreflexe*, 1893.

[84] Tchirjew. *Arch. f. Psych. u. Nervenkrankh*, 1878, **8**, 689.

[85] Ter Meulen. *Zeit f. klin. Med.*, 1882, **5**, 89.

[86] Tuttle. *Journ. Exp. Psychiat*, 1924, **7**, 401.

[87] *Idem Amer. Journ. Physiol.*, 1924, **68**, 338.

[88] Veits. *Brain*, 1920, **43**, 269.

[89] Wacholder and Altenburger. *Arch. f. d. gesam. Physiol.*, 1924, **203**, 620.

[90] Waller. *Journ. Physiol.*, 1890, **11**, 387.

[91] *Idem. Brain*, 1880, **3**, 179.

[92] de Watteville. *Brit Med. Journ.*, 1882, **1**, 736.

[93] v. Weizsacker. *Klin. Woch.*, 1922, **1**, 2217.

[94] Wertheim Salamonson. *Brain*, 1920, **43**, 369.

[95] Westphal. *Arch. f. Psychiat.*, 1875, **5**, 802.

[96] Zenner. *Neurol. Centralb.*, 1886, 316.

[97] Ziehen. *Correspondenz Centralb. d. allg. ärztl. Vereines in Thuringen*, 1887, 1.

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-91, Great Titchfield Street, London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I to XXIII inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.

DECEMBER, 1929

Sec No. ....
Book No ....

BRAIN.

PART 4, VOL. 52.

A STUDY OF A CASE OF CERVICAL GLIOMA.

BY JAMES K. SLATER, M.B., M.R.C.P.EDIN.

AND

F. E. REYNOLDS, M.B.

(From the Department of Clinical Medicine, University of Edinburgh, and the Laboratory of the Scottish Asylums Board.)

(With Plates XIX-XXI.)

THE following case of a glioma involving the cervical portion of the spinal cord is described somewhat fully since, apart from its rarity, the clinical course presented certain very definite difficulties in diagnosis and, further, since the structure of the neoplasm is of considerable interest.

W. D., male, aged 31, a motor mechanic, first consulted Professor Edwin Bramwell on October 20, 1927. The patient had been well until a couple of months previously; he then began to have some pain about the left shoulder, which he was inclined to attribute to a twist while winding up the engine of his car. The pain had gradually got better, but the upper part of his left arm had slowly become weaker; a little later he noticed that the right arm was becoming affected; the weakness in the arms increased progressively. The deltoids, the biceps and infraspinati muscles on both sides showed pronounced weakness with accompanying wasting. The upper parts of both trapezii, the sternomastoids and the pectoral muscles were acting well, but on the left side the action of the lower part of the trapezius was defective. The movements of the hands and of the wrists were unimpaired. On the thumbs, index fingers and outer sides of both fore-arms there was some sensory loss to pain though not to touch. The pupils and palpebral fissures were equal. No deformity, tenderness, or limitation of movement of the cervical spine was present. There was no weakness in the lower limbs; the knee-jerks were hyperactive and equal; the plantar reflexes were flexor in type. The tentative diagnosis made at this time was that of a localized lesion, most probably intermedullary, at the level of the fourth and fifth cervical segments.

On October 28, 1927, the patient was admitted to Professor Bramwell's ward at the Royal Infirmary, Edinburgh. Some days previously he had wakened in the middle of the night with pain in the back of the neck, but this disappeared after he made some movements. The weakness of the arms had become progressively worse till, when examined in hospital, the patient was quite unable to lift the left arm and, with the right arm, movement was possible only below the elbow. On both sides, but to a greater degree on the left side, the deltoid, biceps, brachio-radialias, infraspinatus and supraspinatus were markedly atrophied. The dynamometer readings were: left hand, 90; right hand, 110. There was no inco-ordination or intention tremor and there were no fibrillary tremors of muscles. The wrist and triceps jerks were active and equal on the two sides, but the biceps-jerk was only just perceptible on the right side, and absent on the left. The abdominal reflexes were active. The jaw-jerk was unusually active. Knee and ankle jerks were hyperactive, but there was no clonus. Plantar responses were flexor. Tenderness was elicited on pressure over the fourth cervical spine, but, in contrast to the sensory disturbance present eight days previously, no loss to pain could now be detected in the arms.

On November 1, 1927, the cerebrospinal fluid was examined for Wassermann's reaction and gave a negative result; the globulin was slightly increased in amount; cells were 2 per c.mm.; and the colloidal gold curve was 0012331100. X-ray photographs of the cervical region showed no abnormal appearances.

The patient remained in hospital until January 14, 1928. During the first part of this period pain was occasionally present in the middle line at the level of the fifth and sixth cervical spines, but was controlled by pyramidon, 5 gr. Nearer the end of his stay in hospital, however, the pain was more constantly present and kept him awake at night. Treatment at first consisted of potassium iodide, 25 gr. t.i.d., and mercurial inunction; later; hypodermic injections of strychnine in increasing and decreasing doses were substituted. Some time after the course of injections had commenced the increased tendon reflexes in both legs became more exaggerated. Throughout the patient's stay in hospital the jaw-jerk was always elicited very easily. Before his discharge no additional muscles had become noticeably atrophied, and the weakness in those already affected had become only slightly more marked.

On February 14, 1928, the patient reported. He had suffered a considerable amount of pain in the neck, varying in intensity. The muscular weakness had gradually become more pronounced. Dynamometer readings were: left hand, 60; right hand, 85. There was now a definite extensor response on the left side, but the right plantar reflex was still flexor. The patient had never experienced any difficulty in walking.

On March 10, 1928, the patient again reported. In the interval the neck had become somewhat stiff, but the pain had not been so severe. The weakness in the hands had progressed and both arms were now practically powerless. Dynamometer readings were: left hand, 35; right hand, 60. When walking he experienced a stiffness of the legs and at times he tended to stagger. The plantar reflexes were the same as on the previous occasion.

On April 11, 1928, the patient was readmitted to hospital. The weakness in the left hand had now advanced until it was absolutely powerless. Dynamometer readings were: left hand, 0; right hand, 50. Examination revealed over the limbs and trunk, from the fifth cervical distribution downwards, a general impairment of sensation to pain and temperature, but not to touch. Cerebrospinal fluid was withdrawn simultaneously by cistern and lumbar punctures. The fluid from the lumbar route was xanthochromic and the pressure did not vary either on coughing or on compression of the jugular veins; that from the cisternal route was clear and, on both tests, showed a sharp rise in pressure. Examination of the two fluids showed:—

Lumbar.— Cells = 17 per c.mm. Globulin markedly increased.

Cisternal.—Cells = 2 per c.mm. Globulin—a trace.

Following these punctures the patient experienced considerable pain in the neck and shoulders on both sides, and rapidly became paraplegic with incontinence of bladder and bowel.

The respective contents of the cerebrospinal fluid from the two sources showed that a blockage existed within the spinal theca, somewhere between the cisternal and lumbar regions; from the other clinical data, the level of the lesion was undoubtedly in the neighbourhood of the fifth, sixth and seventh cervical segments.

Professor Wilkie was asked to see the patient with a view to operation, and it was decided to perform an exploratory laminectomy.

On April 19, 1928, the fourth to the seventh cervical spines and laminæ were removed and the underlying dura mater exposed. The membrane looked and felt tense; the normal space between it and the posterior arch was obliterated, but the bony surfaces were not eroded. The third and seventh vertebral arches were then removed. The dura was incised in the mid-line about the level of the fourth cervical vertebra. There was a sudden gush of cerebro-spinal fluid under tension, but it was clear and not pigmented. The incision in the dura was extended to the extremities of the wound and, so far as could be seen, the vertebral canal was filled completely by a growth. The growth was examined above, below, and at the sides, but no point of separation of tumour from cord was found. The tumour consisted of a fusiform expansion of the substance of the cord. Removal therefore was out of the question, and 10 mg. of radium were laid in tubes on the surface (one tube of 5 mg. and five tubes of 1 mg.).

A few hours after the operation the patient died of shock.

Autopsy.—At autopsy the brain, spinal cord and spinal meninges were removed in one piece. The fusiform expansion of the substance of the cord was found to extend from about the third cervical to the first thoracic segment. Laterally, and also posteriorly, between the levels at which the nerve roots entered the cord, nodular swellings were present (fig. 1). The whole tumour was surrounded by the pia-arachnoid membra[illegible]nd at no place was it adherent to the dura mater. Away from the swelling, no abnormality of the spinal cord was observed.

After fixing in formol-ammonium-bromide for a few days, the cord was examined by making transverse incisions at various levels.

Two separate and small hæmorrhages were found, one on each side in the antero-lateral portions of the cord and extending from the sixth cervical to the first thoracic segments. The maximum area of that on the right side occurred in the seventh cervical segment. The hæmorrhage on the left side was smaller in transverse extent than was that on the right side.

In sections taken transversely through the centre of the fusiform swelling, no differentiation into grey and white matter was seen. To the naked eye the medulla was not involved by the neoplasm, but subsequent microscopic examination showed that it had extended for some distance into this region.

Microscopic examination.—(1) A portion comprising the whole transverse diameter was taken from the centre of the fusiform swelling and was placed for twenty hours in Helly's modification of Zenker's fixative and thereafter carried through the routine procedure for paraffin sections. These were stained by Meyer's acid hæmatin and eosin.

(2) Frozen sections of the tissue removed from various levels were impregnated by Cajal's gold chloride sublimate method and by various silver methods.

Sections cut in paraffin and stained by hæmatin and eosin demonstrated that in the centre of the fusiform swelling the entire internal structure of the cord had disappeared, the whole tissue being a mass of protoplasm very rich in nuclei. As compared with the nuclei of the peripheral protoplasm, those in the central parts were small, deeply staining, and were losing their structure (pyknotic changes).

The nuclei of the peripherally situated protoplasm varied in size, the great majority of them were round or oval, large, and rich in chromatin. Some of the oval nuclei were of great size and contained a large amount of deeply staining chromatin.

In certain places the nuclei were grouped together, giving the appearance of a multi-nucleated or polymorpho-nucleated giant cell. In some instances, these groups of nuclei were of the extremely large type (fig. 2).

The structure of the neoplasm, therefore, as demonstrated in paraffin sections, was typical of the "giant-celled glioma of Stroebe."

For the most part, the blood-vessels in the neoplasm were not numerous and their walls were not thickened. In a few instances the smaller vessels contained hyaline thrombi.

Numerous small rounded or oval masses of calcareous material were present in those portions in which the nuclei were undergoing pyknotic changes; the deposition had occurred in the form of small, spherular bodies, and hence the whole mass had a crenated outline. In certain instances the small spherules were discrete and scattered over a rather larger area than that occupied by the aggregations. In other instances the deposition had occurred in the perivascular sheaths of small blood-vessels (fig. 3).

Transverse sections taken from the centre of the fusiform swelling (cervical

PLATE XIX.

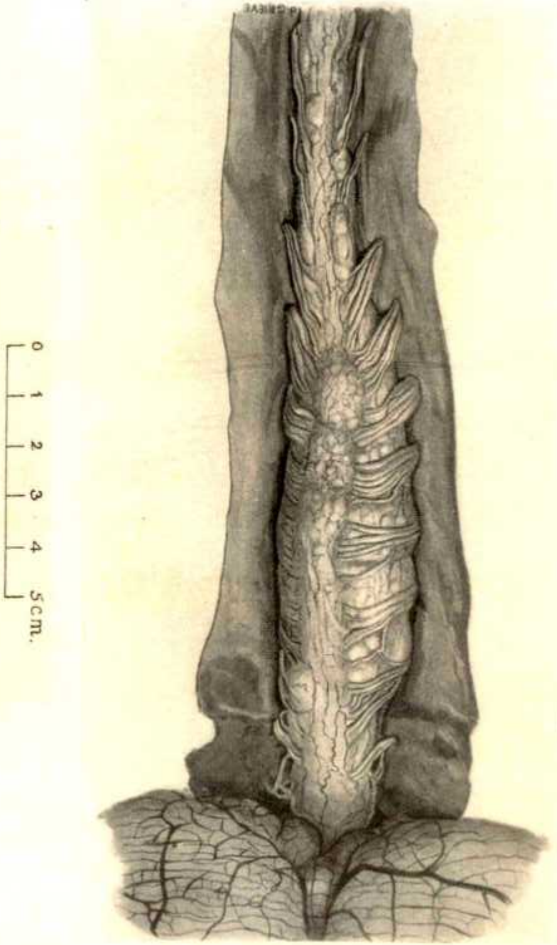


FIG. 1.—Illustrates the fusiform expansion of the cord due to the glioma.

To illustrate paper by James K. Slater and F. E. Reynolds.

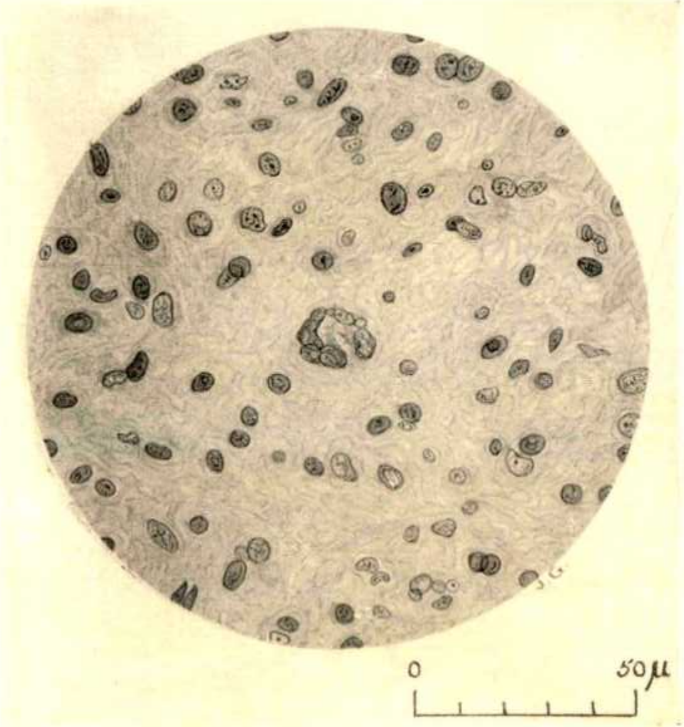


FIG. 2.—Paraffin section stained by hæmatoxylin and eosin. The nuclei, large, round or oval, are rich in chromatin. In the centre of the field they are grouped together, giving the appearance of a multinucleated or polymorphonucleated giant cell.

PLATE XX.

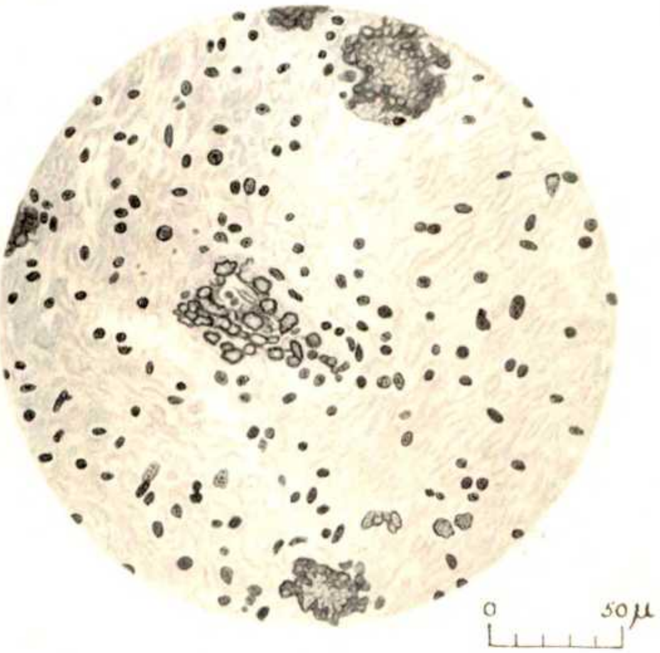


FIG. 3.—Paraffin section stained by hæmatoxylin and eosin. Small globular masses of calcareous material have been deposited in an area of the glioma undergoing necrotic changes. In the centre of the field the deposition is seen to have occurred around a small blood-vessel.

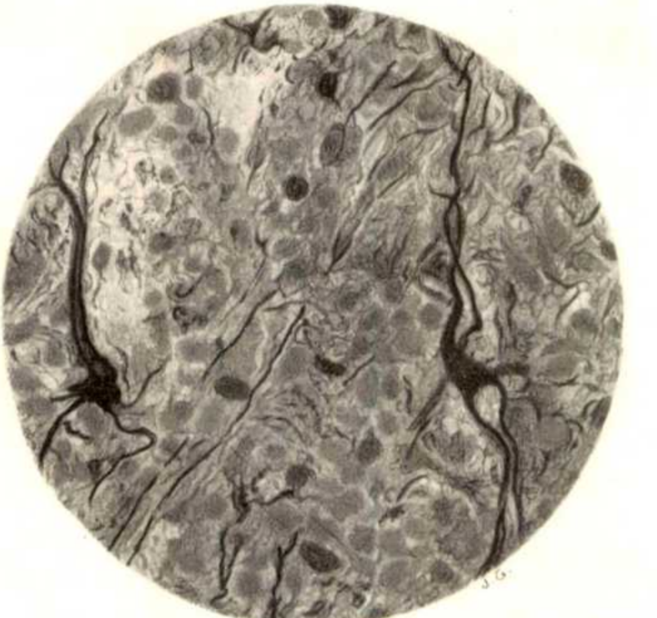


FIG. 4.—Frozen section treated by Cajal's gold chloride sublimate method. Two of the pre-existing astrocytes involved by the glioma are in process of disintegration.

To illustrate paper by James K. Slater and F. E. Reynolds.

segment 6), treated by various silver impregnation methods and by Cajal's gold method, showed that for the most part the neuroglial septa had disappeared, small portions only remaining; no trace of the central canal was seen. A certain number of astrocytes in various stages of disintegration were still present; their bodies and processes were swollen and the latter were to a greater or lesser extent fragmented (clasmatodendrosis, fig. 4).

The structure of the neoplasm was that of a syncytium: numerous large nuclei, varying greatly in size, were embedded in a protoplasmic matrix in which were no cell boundaries (fig. 5).

Transverse sections taken through the lower part of the neoplasm (level of cervical 8 and thoracic 1) showed that the neoplastic growth in the cord was confined to the posterior columns; the membrana superficialis and the septa were intact, but the pia-arachnoid meshes dorsal to the posterior portion of the cord were distended and filled by the neoplasm. In these situations the structure of the neoplasm was of the same syncytial character as was found elsewhere. Serial sections cut in paraffin showed that the neoplasm had reached the pia-arachnoid spaces by infiltrating along the posterior roots.

A cyst some 2 mm. in diameter, due to liquefactive necrosis of neoplastic tissue, was present in one of the posterior columns immediately behind the grey commissure. Its wall was composed of the pre-existing interstitial elements of the cord in which were islands of more or less necrotic neoplastic tissue; it contained fluid with a certain number of fragmented fibres and granular corpuscles.

Paraffin sections showed that certain portions of the tissue around the cyst were very vascular, numerous well-formed blood-vessels being present, and in this area a segment of the wall consisted of very recently proliferated capillaries.

The astrocytes of the grey matter, but particularly those of its antero-lateral portion on both sides, were undergoing very active amitotic proliferation; they were numerous, large, and deeply impregnated by gold; some of them contained two nuclei and many of them were closely approximated in pairs.

Longitudinal sections were made from a portion 2·5 cm. long, comprising the upper part of the spinal cord and lower part of the medulla. These sections showed that strands of the neoplasm had infiltrated upwards; at the lower levels some of the strands were of considerable size. In the medulla they were numerous but narrow, passing between and parallel to the nerve fibres.

Sections prepared by Gross-Bielschowsky's method demonstrated that where the neoplastic tissue was large in amount the majority of the nerve fibres had disappeared. Those which had persisted were greatly atrophied and some of them showed fragmentation (fig. 6). Nodular swelling and the other forms of degeneration of nerve fibres found in experimental lesions (Cajal and others) were not observed.

Longitudinal sections of the lower part of the neoplasm and of the adjacent cord presented a similar picture to the above, the neoplasm extending in the form of wider and narrower strands. Proliferation of astrocytes was again marked, especially in the grey matter which had not been involved by the new growth.

From the above it will be observed that in no part of the neoplasm was there any differentiation of the syncytium into cell elements resembling spongioblasts or astrocytes.

COMMENTARY.

(1) *Pathology.*—It is commonly stated that a glioma rarely, if ever, spreads from the substance of the brain or cord into the pia-arachnoid spaces, whereas an ependymoma of the brain-stem or cord frequently does so. It might be maintained, therefore, that the neoplasm in this case had arisen from the ependyma and not from the neuroglia. Such a differentiation is of no moment, however, since genetically both the ependyma and neuroglia are identical. At most, the so-called "ependymoma" can be considered only as a type of glioma.

The preparations treated by the gold and silver methods demonstrate the neoplasm to be a syncytial glioma throughout The type of neuroglia of which the neoplasm is composed has its counterpart in the earliest form of developing neuroglia present in the neural tube, namely, the syncytium described first by His. The only histological difference between the elements of the neoplasm and of the normal syncytium of the neural tube in its earliest stages is in the increased number and varied size of the neoplastic nuclei and in their large chromatin content.

Had the patient survived longer, it is conceivable that the neoplastic syncytium would have become differentiated into individual neuroglial cell elements, having as their prototypes normal spongioblasts or even astrocytes. It seems probable to us, however, that such differentiation would not have occurred, since it is justifiable to presume that the neoplasm would have continued to extend, but that the relative phases present at the time of death would have been maintained, namely, a progressive zone of newly-formed living neoplasm surrounding a core in which necrotic changes were simultaneously advancing.

In the present case the necrobiotic changes in the central portions of the neoplasm might be explained by the increasing pressure of the growth against the dura mater and surrounding bony canal gradually diminishing the vascular supply and so leading to inadequate nourishment. In general, however, necrosis occurring in neoplasms can be explained only to a certain extent by insufficient blood-supply; some other factor, at present undefined, must come into play.

So far as we are aware, no neoplasm having a structure typical of the "large-celled glioma of Stroebe" has been investigated hitherto by gold and silver impregnation methods. In the present case the latter methods have shown that the structure associated with the "large-celled glioma" is that of a syncytium.

After we had demonstrated, in the present case, the identity of the large-celled glioma as shown in paraffin sections with that of a syncytium, we examined two other cases of Stroebe's neoplasm, paraffin sections of which were in our collection. From these three cases we are convinced that the syncytial character of the neoplastic neuroglia is the true interpretation of the type associated with the term "large-celled glioma."

The deposition of the calcareous material in the present case requires consideration. Deposition of calcareous salts in dead material is a frequent occurrence and, speaking generally, it is quite commonly met with in the portions of neoplasms which have undergone necrosis. Although necrosis occurs almost invariably in parts of gliomata, it is exceedingly rare to find calcareous deposition taking place within it. Why this is so is difficult to explain; calcareous deposition in necrotic tissue is intimately related to fatty material deposited in the process of disintegration. In areas of necrosis in the central nervous tissues, lipoids and other bodies of a fatty nature are found in large amounts, and it might be expected therefore that the brain and cord would be a frequent site of calcareous deposition in conditions in which disintegration of their tissue takes place. Although the large amount of fatty bodies resulting from the disintegration of the elements of the cord may explain the deposition of the lime salts in the present case, it seems to us to shed no light as to why similar deposition does not occur frequently in gliomata.

The last point which we propose to discuss in the pathology of this case is the proliferation of the astrocytes adjacent to the neoplasm.

It has been noted that both at the upper and at the lower ends, where the neoplasm was not occupying the whole area of the cord but was extending in the form of narrow infiltrating processes, the astrocytes in the neighbourhood were undergoing active proliferative changes.

In the majority of those gliomata in which the neoplastic cells become differentiated to the degree of forming astrocytes, it is this change at or near the growing portions which gives rise to difficulty in deciding, firstly, whether the proliferating astrocytes are neoplastic or pre-existing, belonging to the "normal" tissue of the cord, and secondly, whether the change is one affecting the pre-existing astrocytes, causing them to become neoplastic under the influence, as it were, of the neighbouring new growth.

PLATE XXI.

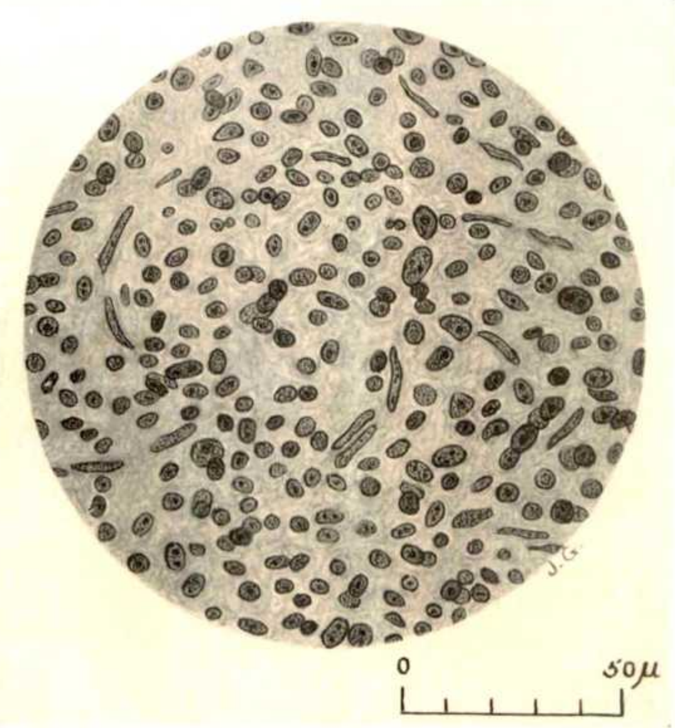


FIG. 5.—Frozen section, treated by Hortega's silver carbonate method, demonstrates the syncytial character of the glioma. (The elongated nuclei are those of the endothelial cells of the blood-vessels.)

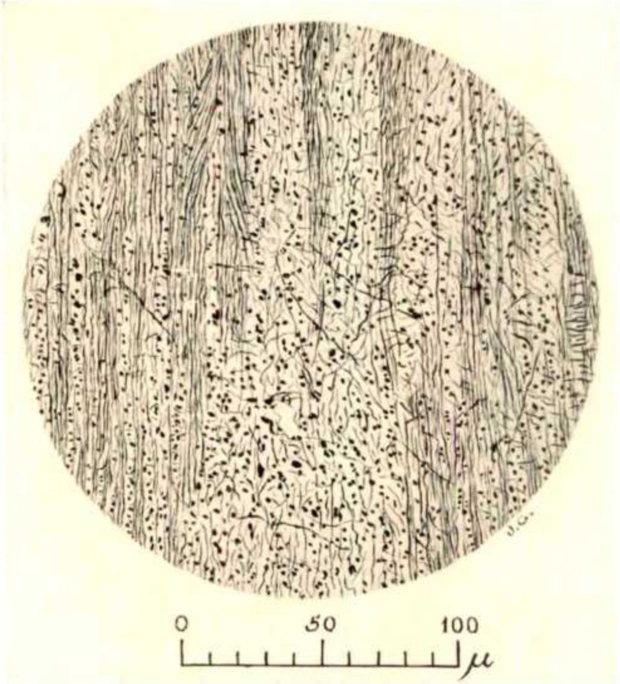


FIG. 6.—Longitudinal section from the upper part of the neoplasm, treated by Gross-Bielschowsky's method, shows the tumour extending in the form of infiltrating strands. The nerve-fibres are atrophying and disappearing.

To illustrate paper by James K. Slater and F. E. Reynolds.

(5) Proliferation of the pre-existing astrocytes of the cord had occurred in the neighbourhood of the syncytial neoplasm. The significance and cause of this phenomenon is discussed.

In conclusion, we wish to express our thanks to Professor Bramwell for supplying us with the clinical records and for permission to publish the present case; further, we wish to acknowledge the valuable help and criticism we have received from him in preparing the case for publication. We wish also to acknowledge the assistance given to us by the Medical Research Council by the aid of a grant towards the expenses of the investigation, and by the Carnegie Trust for financial assistance in publishing the illustrations.

UDY OF THE PATHOLOGY OF A CASE OF GLIOMA CEREBRI.

BY F. E. REYNOLDS, M.B.
(*Superintendent of the Laboratory of the Scottish Asylums Board.*)

(With Plates XXII-XXIV.)

E pathology of the present case of a glioma cerebri follows in l sequence the case published by James K. Slater and F. E. ds in the present volume of *Brain* ("A Study of a Case of ıl Glioma," p. 425). Moreover, the investigation has helped to ı our views as to the unscientific basis of certain classifications mata which have been advanced in recent years, views which ɪeen impressed upon us by the investigation of a considerable r of these neoplasms carried out in the Laboratory of the h Asylums Board.

., male, aged 46, a mining inspector, was admitted to Professor Ritchie's the Royal Infirmary of Edinburgh, on February 3, 1928, complaining e frontal headache, drowsiness, and vomiting. The patient had enjoyed ıt health up to a week before admission to hospital, when the symptoms nmenced suddenly.

examination, the patient was apathetic, but he was not aphasic; dema was marked in both eyes; there was no muscular weakness or lination; the reflexes were present and equal. Wassermann's reaction blood gave a negative result.

e days later, the patient developed a left-sided paresis. He gradually nto coma and, a hypostatic pneumonia supervening, died on February 23, me four weeks after onset of symptoms.

opsy.—The cerebral convolutions on both sides were found to be markedly ıd.

r removing the brain, a medial sagittal section showed the body and the f the corpus callosum to be involved by a neoplasm, but the splenium t been invaded. The portion of the neoplasm situated in the corpus n was pinkish in colour with dark areas of necrosis (Plate XXII, fig. 1). ittal sections were made through each hemisphere. On the *right* side, plasm, which was rather paler in colour than the cerebral tissue, d diffusely both in an antero-posterior and in a lateral direction,

(5) Proliferation of the pre-existing astrocytes of the cord had occurred in the neighbourhood of the syncytial neoplasm. The significance and cause of this phenomenon is discussed.

In conclusion, we wish to express our thanks to Professor Bramwell for supplying us with the clinical records and for permission to publish the present case; further, we wish to acknowledge the valuable help and criticism we have received from him in preparing the case for publication. We wish also to acknowledge the assistance given to us by the Medical Research Council by the aid of a grant towards the expenses of the investigation, and by the Carnegie Trust for financial assistance in publishing the illustrations.

A STUDY OF THE PATHOLOGY OF A CASE OF GLIOMA CEREBRI.

BY F. E. REYNOLDS, M.B.
(*Superintendent of the Laboratory of the Scottish Asylums Board.*)

(With Plates XXII-XXIV.)

THE pathology of the present case of a glioma cerebri follows in natural sequence the case published by James K. Slater and F. E. Reynolds in the present volume of *Brain* ("A Study of a Case of Cervical Glioma," p. 425). Moreover, the investigation has helped to confirm our views as to the unscientific basis of certain classifications of gliomata which have been advanced in recent years, views which have been impressed upon us by the investigation of a considerable number of these neoplasms carried out in the Laboratory of the Scottish Asylums Board.

J. D., male, aged 46, a mining inspector, was admitted to Professor Ritchie's ward in the Royal Infirmary of Edinburgh, on February 3, 1928, complaining of severe frontal headache, drowsiness, and vomiting. The patient had enjoyed excellent health up to a week before admission to hospital, when the symptoms had commenced suddenly.

On examination, the patient was apathetic, but he was not aphasic; papillœdema was marked in both eyes; there was no muscular weakness or inco-ordination; the reflexes were present and equal. Wassermann's reaction on the blood gave a negative result.

Some days later, the patient developed a left-sided paresis. He gradually passed into coma and, a hypostatic pneumonia supervening, died on February 23, 1928, some four weeks after onset of symptoms.

Autopsy.—The cerebral convolutions on both sides were found to be markedly flattened.

After removing the brain, a medial sagittal section showed the body and the knee of the corpus callosum to be involved by a neoplasm, but the splenium had not been invaded. The portion of the neoplasm situated in the corpus callosum was pinkish in colour with dark areas of necrosis (Plate XXII, fig. 1).

Sagittal sections were made through each hemisphere. On the *right* side, the neoplasm, which was rather paler in colour than the cerebral tissue, extended diffusely both in an antero-posterior and in a lateral direction,

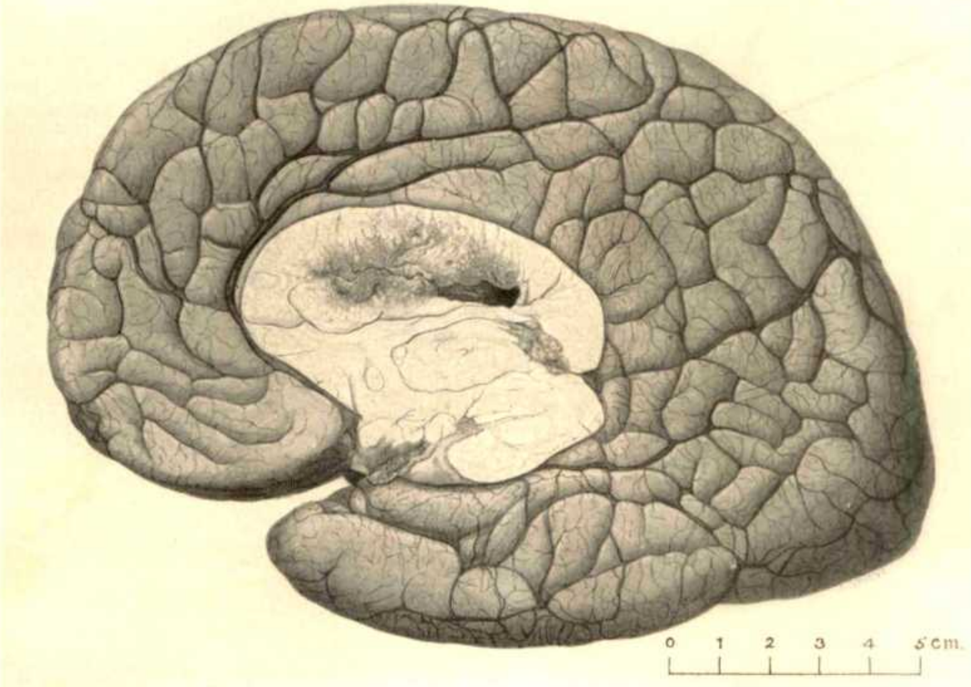


FIG. 1.—Medial sagittal section showing involvement of the body and knee of the corpus callosum by the glioma.

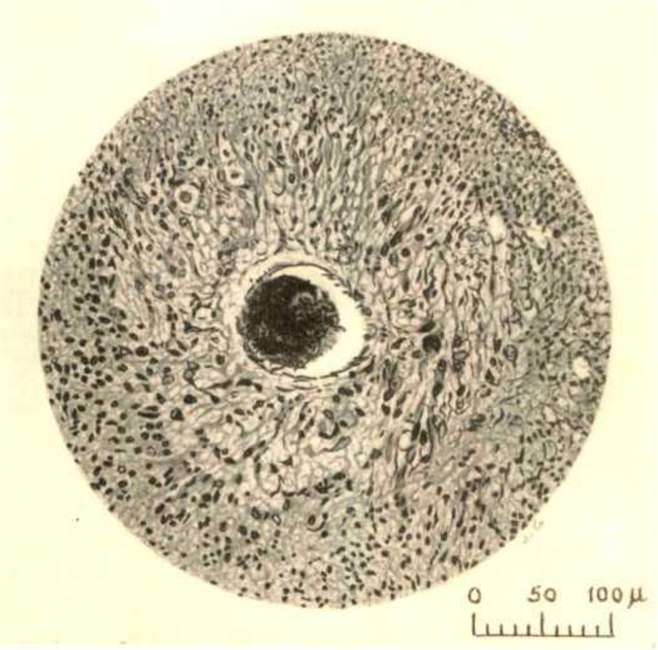


FIG. 2.—From a necrosing portion of the glioma. The neoplastic tissue immediately around the central blood-vessel is still living, whereas that more distant is necrosed. The phenomenon is that of the so-called "pseudo-rosette." Frozen section treated by Hortega's silver carbonate method.

To illustrate paper by F. E. Reynolds.

PLATE XXIII.

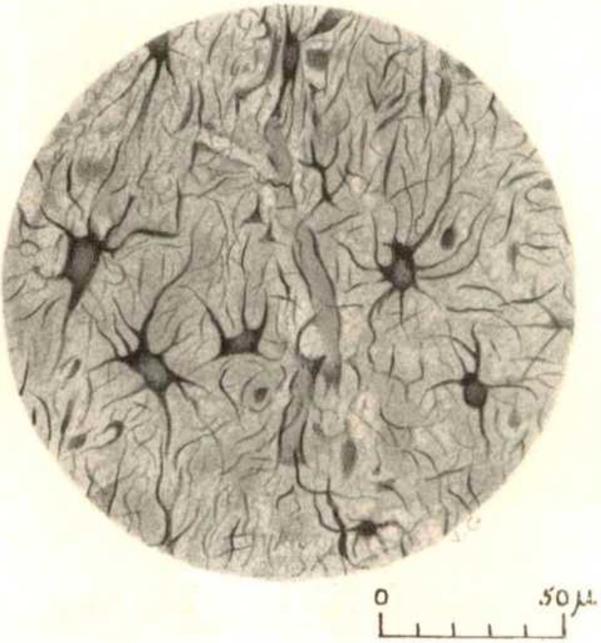


FIG. 3.—From the neighbourhood of the corpus callosum. The neoplastic astrocytes are large and numerous, and have reached a high degree of differentiation. Frozen section treated by Cajal's gold chloride sublimate method.

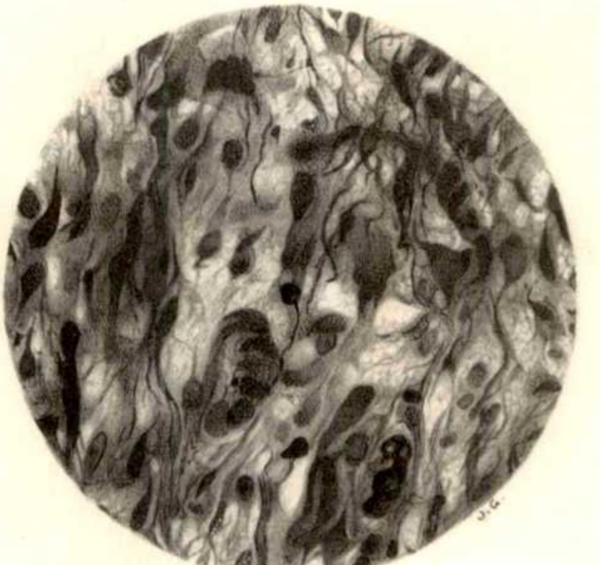


FIG. 4.—From the peripheral portion of the glioma. Some of the neoplastic cells are elongated, resembling the spongioblasts of the developing central nervous system. Frozen section treated by Hortega's silver carbonate method.

To illustrate paper by F. E. Reynolds.

involving a considerable portion of the white matter, but its limits were not well defined to the naked eye, the obviously neoplastic tissue merging into that which appeared "normal." A hæmorrhage rather more than 1 cm. in diameter was situated in the subcortical white matter in the neighbourhood of the precentral gyrus, 1·5 cm. below the surface; the extravasated blood was dark red in colour and the clot was very loosely held together. The tissue lying deep to the hæmorrhage was considered to be neoplastic, but that superficial showed no macroscopic change from the normal. (Later microscopic examination revealed, however, that neoplastic tissue was present superficial to the hæmorrhage, and had invaded the cerebral cortex.)

On the *left* side, the neoplasm had invaded the white matter of the hemisphere in a similar manner, but as far as could be seen it was not so extensive as on the right side.

Microscopical examination.—Portions of tissue were taken from each side about 2 cm. from the middle line, and, having been divided into pieces of suitable size, were fixed in Helly's modification of Zenker's solution. Thereafter the pieces were carried through the routine procedure for paraffin sections and were stained by Meyer's acid hæmatin and eosin and by Heidenhain's Azan method.

Pieces of tissue were taken from various portions of the neoplasm, including those near the corpus callosum and those near the periphery in the neighbourhood of the subcortical hæmorrhage and were fixed in formol-ammonium-bromide solution. Frozen sections made from these were treated by Cajal's gold chloride sublimate, by Hortega's silver carbonate and other silver impregnation methods, and by Morgan's method for demonstrating myelin sheaths.

(1) Sections of the more central parts cut in paraffin and stained by hæmatin and eosin and by the Azan method showed the neoplasm to be a glioma rich in nuclei. The nuclei varied in size, the average being considerably larger than that of a normal astrocyte, and they contained a large amount of chromatin.

Throughout the sections were many areas of necrosis. These areas consisted of a central mass of granular and structureless material surrounded by a zone in which the neoplastic nuclei were pyknotic and in various stages of disintegration. This appearance, therefore, was that frequently referred to by authors as the "palisade arrangement."

In many instances, the neoplastic cells immediately around a blood-vessel were not necrosed, but the tissue situated more distal had disintegrated; thus the picture presented in these portions was that of the so-called "pseudo-rosette" (fig. 2).

The walls of most of the arterioles were thickened, the thickening being chiefly in the inner coat, although considerable fibrosis was present in the muscular coat. In many cases, thrombosis of smaller blood-vessels had occurred and in some of these the thrombus had been organized into hyaline fibrous tissue.

(2) (*a*) Sections taken from the neighbourhood of the corpus callosum and

treated by Cajal's gold chloride method demonstrated this portion of the glioma to be composed of numerous large astrocytes which had reached a high degree of differentiation. Many of their processes were long and thick, and some of them were seen to come into relationship with blood-vessels, but vascular foot-plates were not well formed. Occasionally a fibre had developed in one of the processes, but for the most part the neoplastic astrocytes were of the protoplastic type (fig. 3).

At some distance from the main mass of the portion of the glioma involving the corpus callosum, small groups of fibrous astrocytes were seen which were large and with thickened processes, but which showed structural perfection; some of them contained two nuclei, being in a state of amitotic division.

At the periphery of the necrotic areas the neoplastic astrocytes were swollen and their processes were fragmenting ("clasmatodendrosis").

(*b*) Sections taken from the peripheral portions of the glioma, treated by Cajal's gold chloride and by Hortega's silver carbonate methods, demonstrated that differentiation of the neoplastic cells was not nearly so advanced as in the central portions. The nuclei were numerous and showed great variation in size, some of them being exceedingly large.

In certain areas some of the neoplastic cells were elongated, resembling the spongioblasts of the developing central nervous system (fig. 4). In other areas the structure was that of a syncytium, numerous large nuclei being embedded in a protoplasmic matrix (fig. 5).

The pre-existing astrocytes involved by these actively growing portions of the neoplasm were undergoing clasmatodendrosis (fig. 6).

(3) Sections of the peripheral portion of the neoplasm, stained by Morgan's method, showed that the myelin sheaths had disappeared in the neoplastic area. At the extreme periphery of the neoplasm a certain number of them persisted, but they were irregular in outline and the myelin had disintegrated into droplets.

(4) Sections of the peripheral portions of the neoplasm, stained by Gross-Bielschowsky's method, showed nerve-fibres persisting in the neoplasm for a considerable distance below the cortical layers, and a certain number of them were present in those portions of the neoplasm which were necrotic. In these areas many of the nerve-fibres present showed nodular swellings and were disintegrating into granules.

COMMENTARY.

Many of the pathological problems raised by the case now published have been discussed in the paper by Slater and Reynolds to which references has been made already. To avoid needless repetition, these points will be referred to only so far as they require amplification in view of the differences in the histological picture of portions of the glioma which forms the subject of the present publication.

PLATE XXIV.

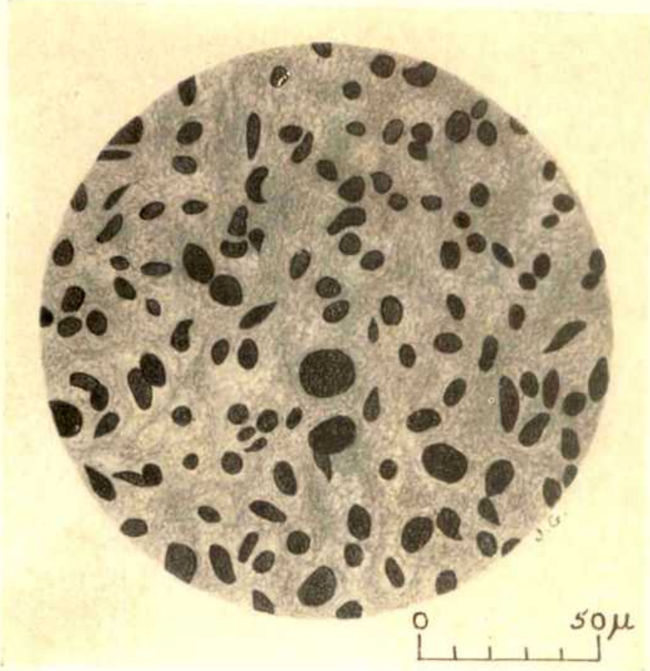


FIG. 5.—From the peripheral portion of the glioma. The structure is that of a syncytium, numerous large nuclei being embedded in a protoplasmic matrix. Frozen section treated by Hortega's silver carbonate method.

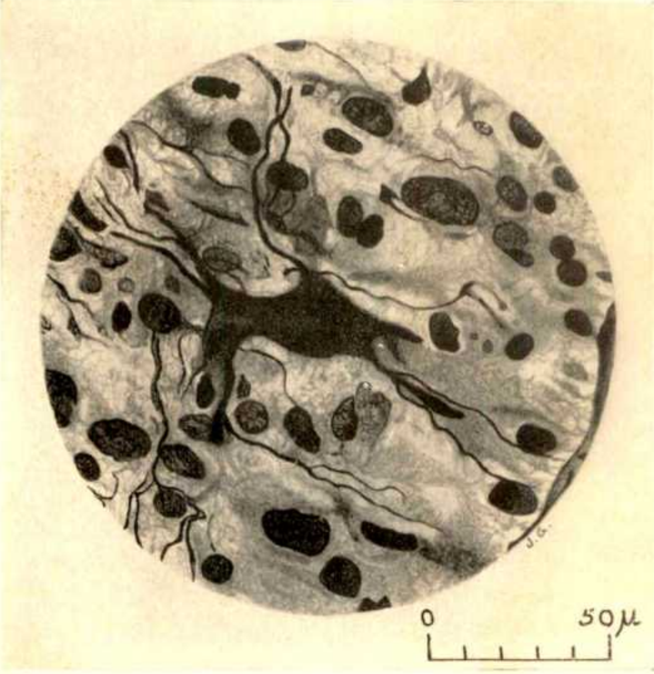


FIG. 6.—From the peripheral portion of the glioma. The processes of pre-existing astrocytes, involved by the actively growing neoplasm, are swollen and disintegrating ("clasmatodendrosis"). Frozen section treated by Cajal's gold chloride sublimate method.

To illustrate paper by F. E. Reynolds.

From the comparatively large amount of necrosis present, and the high degree of specialization reached by the neoplastic astrocytes, there is no doubt that the portion of the glioma in and around the corpus callosum was of older standing than the peripheral portions. Further, whereas the cells in the older parts had passed into a quiescent phase, the elements in the peripheral portions were in a very active vegetative condition.

The glioma had arisen, therefore, in the central portions of the brain and had extended widely in both cerebral hemispheres. The structure of the actively growing peripheral portions was largely that of a syncytium, and the only differentiation of the elements near the periphery was into cells, having as their prototype the spongioblasts of the developing central nervous system.

Hence the gliomatous elements showed all degrees of structural differentiation from the syncytium to cells having a very close resemblance to the fully developed normal astrocyte.

The demonstration of the manner of growth of the glioma which is the subject of the present paper, namely, a syncytial infiltration of the surrounding cerebral tissue, explains the difficulty experienced in differentiating by the naked eye between the normal cerebral tissue and the adjacent neoplastic glia.

It is probable that many gliomata grow as a syncytium. Veszpremi (*Virch. Arch.*, 213) maintained that in the majority of cases the glioma has a syncytial character in its actively growing peripheral parts, whereas in the older central portions the elements had differentiated into individual isolated cells.

Under the microscopic examination of the present case, it was noted that at some distance from the neoplastic tissue small groups of enlarged fibrous astrocytes were present, and that some of them were even in a stage of division. That these astrocytes were pre-existing cells and not those of an invading process of the glioma, which had been cut transversely, was concluded not so much from their position in relation to the neoplasm as from the structural perfection which they represented.

The significance and explanation of groups of astrocytes similar to those described has been discussed in the paper by Slater and Reynolds (loc. cit., p. 432).

The present case well illustrates the necrosis which is so common a feature in gliomata. Death of the cells is due probably to a number of factors; of these, an insufficient nourishment of the cells is present in most instances and results, firstly, from the rapid proliferation of the neoplastic cells causing the tumour to outgrow the blood supply, and secondly, as demonstrated in this case, to thrombosis of blood-vessels in the neoplasm. On general principles, the thrombosis occurs owing to injury of the endothelium lining the lumen of the blood-vessel, and hence the question arises as to the nature of the agent which causes the damage.

It is an anatomical fact that every astrocyte, normal or neoplastic, has at least one, but probably more, of its processes which comes into relationship with the perivascular adventitial lymph sheath of the blood-vessel and which enters into the formation of the membrana limitans perivascularis. We are of opinion that as a result of this anatomical relationship, in the case of the astrocyte, absorption and excretion of metabolic substances occur through these processes (Reynolds and Slater, *Edin. Med. Journ.*, 1928, p. 54). During rapid reproduction of the cells, not only are metabolic products excreted into the perivascular lymph clefts in much larger amounts than under normal conditions, but in the case of neoplastic cells it is known that the chemical nature of their effete products differs from those of the normal cell. It is justifiable to presume that the mechanism by which the waste products are drained away, while sufficient for more ordinary conditions, cannot cope with the great excess of excretion. Consequently the fluid in the perivascular lymph spaces becomes saturated with these waste products, and we suggest that it is their presence together, possibly, with their altered chemical nature which is responsible for the damage to the vascular endothelium

Lastly, it seems appropriate to discuss very briefly the classification of gliomata. Of late years, the tendency has been to divide these neoplasms into more or less numerous classes. These classifications are based on the varied histological picture presented by the neoplasms, But such a division is necessarily artificial and, as in the present instance, gliomata occur which present all stages of structural development, from the simplest—namely the syncytium—to the most complex—namely the astrocyte.

It seems better to us, therefore, to interpret the structure of gliomata along lines of progressive specialization of their elements as indicated in the present paper, rather than to attempt to allocate them to a particular structural category.

From the point of view of determining and interpreting the structure of a glioma, the present case illustrates the necessity, firstly, of placing material of suitable size into fixative as soon as possible after death, so that it may be examined adequately by gold and silver impregnation methods; and, secondly, of examining different portions of the glioma.

SUMMARY.

(1) The present study is of a large glioma cerebri which began in the central portion of the brain and extended widely into both cerebral hemispheres.

(2) The older parts of the neoplasm consisted of astrocytes which had attained a high degree of specialization, whereas the actively extending and recently formed portions were composed of a syncytium and of cells having as their prototype the spongioblasts of the developing neural tube.

(3) At some distance from the neoplastic tissue, there were small groups of pre-existing astrocytes which were proliferating.

(4) Necrosis in the neoplasm was due probably in part to its outgrowing the blood supply and to the accumulation in the tissues of the waste products of neoplastic metabolism.

(5) It is better to interpret the structure of gliomata along lines of progressive specialization of their elements rather than to allocate them to a particular structural category.

In conclusion, we desire to express our thanks to Professor Ritchie for giving us the opportunity of investigating the pathology of the case and for his permission to publish the results. We are indebted to the Medical Research Council for a grant towards the cost of the research and to the Carnegie Trust for financial assistance in publishing the illustrations.

THE CORPUS CALLOSUM AND ITS TUMOURS.

BY REDVERS IRONSIDE,
London,
AND
MANFRED GUTTMACHER,
Baltimore.

		PAGE
I.	Historical Introduction	442
II.	Anatomical Considerations	445
III.	Physiological Considerations	448
IV.	Discrepancies between Physiology and the Known Clinical Picture of Pathological Lesions	454
V.	Report of Fourteen Cases	454
VI.	Localization within the Corpus Callosum	477
VII.	Differential Diagnosis	477
VIII.	Pathology	478
IX.	Treatment	480
X.	Bibliography	480

Historical Introduction.

In the year 1675, Wepfer, the Professor of Medicine at Tübingen, published his famous "Apoplexia." In this book (Case history 14) is recorded what must be one of the first tumours of the corpus callosum ever reported. A perusal of this history gives a picture of the neurology of the era of Willis, Boerhaave, Haller, Sydenham, Morgagni, Valsalva and Meade, which is hardly equalled by the dissertations of any modern writer.

Ursula Aberlin, of Wolfach, a virgin, aged 23, was a maidservant to the innkeeper "At the Sign of the Sun." In the year 1667, one day she carried home from the field a ponderous bag of grain on her head. She suddenly had a sensation as though something had burst within her head. She was, however, able to continue uphill and perform her errand, but "from this time she was less capable of retaining her urine, yet no one excelled her in her accustomed duties as a servant-maid, neither putting off strenuous affairs to some other time, nor putting her labours upon her sturdier employer. Six months later," continues Wepfer, "having no presentiment of anything evil, at the hour when the cock crows, she thought herself unable to stand firmly on her left foot. Her whole left side soon became deprived of motion and sensation, her lips were twisted, her maxilla deviated to the right. As soon as she was able, she spoke intelligently; indeed, only a short time after her very desperate state. She then lapsed into a delirium for several days and complained of the most raging pain in the top of her head, and the right eye pained most intensely, as though it were being evulsed from its orbit." Her frequency of micturition became more marked and there was, apparently, polyuria, without, however, incontinence. "On February 1, 1668, at the request of the illustrious Anna Magdalene, the Countess of Fürstenburg, I was called to see the girl. Eight weeks after her hemiplegic ictus she was still fat and of good colour, her mouth was no longer distorted and she spoke sensibly and quickly. She was no longer harassed by the intense headache. Although unable to move her left arm spontaneously, when one or other of her digits was forcibly flexed and compressed by me against the palm, she withdrew her arm a very little distance towards her.[1] She was unable to move her left foot. At that time, however, her left arm and leg were often flung up in a convulsive movement." Power gradually returned to her hemiplegic limbs, but six months later headache and giddiness returned. Gradual failure, with amenorrhœa, followed, and eighteen months after the onset of her illness "she grew delirious for many days," but just before her death she became rational. Always, even to her last breath, she saw and heard accurately. On March 24, 1669, she died. "By entreaty and money," says Wepfer, "I obtained the opening of the cadaver on March 25th." He found a cystic degenerating tumour of the posterior part of the corpus callosum, extending into the right lateral ventricle and the right internal capsule.

We have been able to find only one case report of an earlier date than this, reported by Felix Plater, Professor of Medicine at Basle, in his "Observationum," under the heading, "Stupor or Obfuscation from a Globular Tumour Occurring in the Brain." This case report is of some interest, as it gives an account of the apathy and lethargy characteristic of many growths of the corpus callosum. A study of the pathological report on this case, in the light of retrospect, indicates that the tumour was probably a hæmangioma of the falx, involving the corpus callosum.

"Caspar Bonecurtius, a Knight, gradually, over the course of two years, became mentally deranged, until finally he was utterly incapable of any reasoning. He did not ask for food and it was difficult to force him to eat; nor, unless coerced, did he seek his bed, but continually sat with his arms on the table, supporting his head with his hands. There he was wont to sit, almost asleep, neither asking questions nor volunteering any information spontaneously. Occasionally, he uttered a few words but they were hardly relevant. These things having gone on in this state for half a year, he suddenly died." At autopsy, a globular tumour "the size of a small apple" was found over the corpus callosum. It was composed of masses of tortuous venules.

---

[1] An interesting foreshadowing of Leri's reflex.

Soye, in 1698, in the "Extraits du Journal des Savants," described a case characterized by epileptiform convulsions.

Morgagni, in 1740, in the "Epistolae" appended to the works of his great master, Valsalva, described a case with great mental slowness, lethargy, and gradually oncoming right-sided weakness; and in 1741, La Peyronie described two cases with lethargy, apathy and mental defect and, in one of the cases, epileptiform convulsions.

We see that, while some of the salient features of tumours of the corpus callosum have been known for nearly 300 years, these observations had no real pertinence in the historical development of the clinical diagnosis. Before Bristowe's establishment of the "Callosal Syndrome" in 1884, no serious efforts seem to have been made to make the diagnosis during life.

The first attempt to formulate a syndrome was that of J. S. Bristowe, who published his observations in this Journal forty-five years ago.

Bristowe stressed:—

(1) The ingravescent character of the symptoms—a progressive hemiparesis with vague motor symptoms on the contralateral side.

(2) The supervention of apathy, associated for the most part with extreme drowsiness, a puzzled, inquiring look, difficulty in swallowing and cessation of speech. He stated that this seemed due, mainly, to a stupidity and an irresistible tendency to sleep. He never noticed a true aphasia.

(3) The absence of cranial nerve palsies.

(4) The slightness of headache and vomiting.

This work remains the inspiration of all subsequent work on this subject, both in this country and abroad. In England and America less attention has been paid to tumours of the corpus callosum than on the Continent. Of recent years the most important contributions to the subject have been those of the Italian school, including Mingazzini's monograph, "Der Balken," published in 1922; a more recent paper by his pupil Balduzzi, in the *Archiv für Psychiatrie und Nervenkrankheiten*, in 1926; and Ayala's article, published in 1915.

The more important contributions of the French school are the Paris Thesis of Levy-Valensi, published in 1910, and the papers of

Raymond. To the "syndrome" of Bristowe, Schüpfer, in 1899, added the idea of localization within the corpus callosum, according to whether the neoplasm occupied the genu, the tapetum or the splenium. Raymond, in 1906, added a detailed account of the psychical changes which had been observed in tumours of the corpus callosum, and Liepmann, in 1907, described the symptom of apraxia in callosal lesions.

Balduzzi, in the most recent paper published in German, in 1926, reviews 115 cases of tumour of the corpus callosum, collected from the literature. Up to the present time no writer has contributed more than four individual cases. With the wealth of clinical material which is available at the National Hospital, Queen Square, London, and the Johns Hopkins Hospital, Baltimore, we are able to put on record in this paper fourteen additional cases previously unpublished. The diagnosis of tumours of this part of the brain has been made but rarely during life. The present paper is an attempt to define more clearly the symptomatology and signs of tumours in this region.

ANATOMICAL CONSIDERATIONS.

The corpus callosum is the chief inter-hemispherical association system between the two halves of the neopallium. There are, however, other commissures, namely, the anterior commissure, the massa intermedia and the posterior white commissure, which may, as Lewandowski first pointed out, functionally replace a damaged, or partially destroyed, corpus callosum.

The corpus callosum is seen, on medial sagittal section of the brain, to form an arched structure about 10 cm. long. Its anterior end is about 4 cm. from the frontal pole, and its posterior end about 6 cm. from the occipital pole of the hemisphere. It is wider and broader posteriorly.

The superior surface is traversed by numerous transverse ridges and furrows, and is covered by a thin layer of grey matter, the indusium, which exhibits on either side of the middle line the medial (nerves of Lancisi) and lateral longitudinal striæ.

The medial striæ may be traced round the genu and rostrum to the gyrus sub-callosus. The lateral striæ may be followed into the area parolfactoria and the anterior perforated spot. Caudally, these striæ, as well as the indusium, pass round the splenium into the gyrus dentatus. The investing grey matter of the corpus callosum and the two sets of striæ represent the remnants of an atrophic olfactory convolution, which has gradually been reduced in size as a result of the progressive development of the corpus callosum in mammals.

A corpus callosum may be observed in the animal series from marsupials to man, and its development in size is parallel with the phylogenetic development of the neopallium. With the assumption of the erect posture by the higher apes, olfactory sensations took a less prominent place than heretofore, and the rhinencephalon gave way to the development of inter-hemispherical association fibres connecting both halves of the neopallium, which was ever-increasing in size and complexity. Marshall pointed out that the corpus callosum was twice as large in man as in the chimpanzee, and he associated this with the development of the functions of speech, the development of psychical functions and the increase in size of the neopallium.

Spitzka found that the area, depth and length of the corpus callosum in higher apes, negroes and white people, increased with the degree of mental development. He found that the area of cross-section of the corpus callosum was greater in those of average intelligence than in the feeble-minded, and actually claims that measurements of the corpus callosum may indicate the degree of intelligence.

In man the corpus callosum, the fornix and the anterior commissure begin to develop about the fourth month of fœtal life. The lower part of a thickening in the lamina terminalis differentiates first into the anterior commissure, later into the anterior part of the fornix, and afterwards its posterior pillars are formed. Finally, the corpus callosum appears, its anterior part being the first developed, and its growth extending backwards with the development of the hemispheres.

Mingazzini's researches on the myelination of the corpus callosum in the human fœtus are of interest. He distinguishes three stages: (1) During intra-uterine life no myelin fibres can be seen in the corpus callosum. From the second week to the end of the second month of extra-uterine life myelination begins. (2) From the third to the seventh month myelination of the transverse fibres appears in the lateral regions and in the superior and inferior aspects of the corpus callosum. 3) Myelination becomes complete about the twentieth month of extra-uterine life. The longitudional fibres lying most medially are the last to become myelinated.

Mingazzini's studies show that the transverse fibres originate from large and small pyramidal cortical cells as association fibres: von Muratow says exclusively from large pyramidal cells. Other fibres represent the collaterals of long projection tracts, or are bifurcations of association fibres. It may be taken as the current consensus of opinion that in the adult the commissural fibres connect homologous and heterologous cortical areas. This work of Mingazzini has recently been confirmed in the main by Villaverde. The *genu* contains fibres uniting the frontal convolutions of the two hemispheres. The *body* of the corpus callosum contains fibres uniting on the two sides, the first frontal and the pre-central convolutions, the parietal lobes, the para-central lobules and the insulæ. The *splenium* contains fibres uniting the parietal lobes, the occipital convolutions, the lingual lobes and the angular gyri. In the main the transverse fibres constitute inter-hemispherical connections between identical areas of the brain.

One is reminded of the controversy which disturbed the neuro-anatomists at the end of the last century. Meynert believed that the fibres connected only homologous areas of the hemispheres. He claimed that he had traced individual fibres from one side to the other, and his opinion was supported by Reil and Arnold.

One of the most important workers on the morphology of the corpus callosum was David Hamilton, the Professor of Pathology at Aberdeen. In 1885 he published the results of years of labour on the structure of the corpus callosum, enunciating the then heterodoxic view that the corpus callosum carried fibres to the opposite thalamus, caudate nucleus, internal and external capsules, the optic and olfactory tract and the temporal lobe. He believed that these fibres decussated in the mid-line, crossed to the external part of the corpus callosum, going upwards and outwards, and then turning downwards, towards the lenticular nucleus, where they divided into an inferior group going to the internal capsule and a superior to the external capsule. Moreover, he failed to find positive evidence that the corpus callosum connected any two homologous cortical areas. Hamilton, modestly enough, gave Gratiolet and Foville priority for some of these views, but with them, however, they were really mere speculations, and, in all fairness, Hamilton must be called the originator of this doctrine. Hamilton worked on human adult and embryo brains. In this investigation he made use of his now forgotten method of "mezzoscopy." The brain was treated by gelatine and potash; the fibres swelled from one third to twice their normal size, so that they could be nicely distinguished by a hand lens.

In England, Beevor, supported by investigations on monkeys and marmoset embryos, opposed Hamilton bitterly. In 1899 Sherrington performed cortical ablations in monkeys, and found that, in the corpus callosum, fibres "tend to scatter and do not pass chiefly between identical areas of the two hemispheres." These results were substantiated in 1901, by Lyndon Mellus working in Horsley's laboratory.

Bianchi and D'Abundo, as the result of cortical ablation experiments performed in 1886, on dogs and cats, postulated the existence of a tract going from the cortical motor area through the opposite internal capsule, returning to its original side by a lower crossing in the pyramidal decussation.

Wallenberg, working on the pole-cat, Bechterew and Ugolotti and von Mayendorf, all traced projection fibres to the opposite internal capsule, but Dejerine, and more recently Levy-Valensi in his "Anatomical Researches," published in 1910, were unable to demonstrate such projection fibres.

At the Düsseldorf Annual Meeting of the "Gesellschaft Deutschen Nervenärzte," held in September, 1926, Mingazzini, who for many years has kept a constant interest in this subject, read a paper—"The Relations between the Corpus Callosum, the Lenticular Fibres and the Internal Capsule." This was the result of a study that he had made with Gianelli on the brain of an idiot who had suffered since birth from a right spastic hemiplegia. They concluded that "a very considerable proportion of the corpus callosal fibres which originate from the right hemisphere bend round the left caudate nucleus and contribute to the formation of the left internal capsule."

The relation of the longitudinal tracts running under and alongside of the corpus callosum to its integral fibres is still unclear. It is most likely that (1) the fasciculus sub-callosus, and (2) the fasciculus occipito-frontalis, are structures entirely separate from it. The question as to whether the fasciculus callosum longitudinalis is a definite part of the callosal system is more uncertain.

In conclusion, one may state the present-day opinion as being (1) that the commissural fibres arise from large pyramidal, small pyramidal, and polymorphous cells of the cortex (Cajal) and unite homologous and heterologous areas of the two hemispheres; (2) that definite bundles of callosal projection fibres pass from the hemispheres to the internal capsule of the opposite side.

PHYSIOLOGICAL CONSIDERATIONS.

The corpus callosum appears to have been first recognized by Galen at the beginning of the first century A.D. Fifteen hundred years later this structure was selected by La Peyronie, the Professor of Surgery at Montpellier, as the "seat of the soul." La Peyronie's pronouncements were received with great attention, and the stamp of finality seemed to be placed upon his hypothesis when Giovanni Maria Lancisi, physician of several Popes, gave it his support in his "De Sede Cogitantis Animae," which he wrote in 1718. By this time Willis had undertaken researches on the structure of the corpus callosum, and Sir Christopher Wren's beautiful engraving of Willis's dissection of the corpus callosum may be seen in the 1664 edition of the great anatomist's "De Cerebri Anatome."

In 1749, the experimental method of study of the corpus callosum was commenced by Haller's favourite pupil, Johann Gottfried Zinn, who published at Gottingen in his 21st year a brilliant monograph which is an orderly and logical piece of experimental work on the corpus callosum of dogs. He found that section of the corpus callosum produced lethargy and later paralysis of the limbs, at first confined to one side, later bilateral. As a result of the six experiments, however, he concluded that "the corpus callosum may be damaged and cut, yet the senses and power of movement remain intact." It is interesting to note, in reviewing his protocols, that lethargy seems to have been an almost constant symptom in his animals. Other earlier experimenters were Vieussens, Perrault and Karpius, Petit, Valsalva and Saucerotte. The results of these earlier workers were almost certainly marred by the occurrence of secondary infection.

Between 1830 and 1850, Lorry, Longet, Magendie and Flourens, all made total sections of the corpus callosum with negative results. The operation is by no means a simple one, and most workers have had a high operative-animal mortality. The usual difficulties in appreciating psychical changes in animals are present. No recent worker has obtained clear-cut disturbances of motility following section, and the majority of workers—Franck and Pitres, and Dotto and Pusateri working on cats, Monaco and Koranzi on dogs, and Levy-Valensi on monkeys, have been unable to observe any effect on the psychic behaviour of their animals.

In 1893, Muratow published the results of his experiments on dogs, which fit in beautifully with our clinical experience of the effects of lesions in man. Only three of his animals survived section of the corpus callosum. He found these animals sleepy and apathetic. They were badly orientated and paid no attention to their surroundings. They maintained uncomfortable postures in which they were placed. Their gait was inco-ordinated and uncertain. They did not appear to see obstacles placed directly in front of them and stumbled over them. Although Levy-Valensi has produced an essentially similar picture in dogs—stupidity and apathy, the forgetting of many tricks and apraxia—by longitudinal section of the corpus callosum, we may hesitate to accept these results without further confirmation.

In 1887, Brown-Séquard performed electrical stimulation of the corpus callosum; he found that the current had to be stronger than that needed to excite the Rolandic area, and he concluded that every part of the corpus callosum had fibres capable of giving movements on stimulation.

Lewandowski put forth the theory that the corpus callosum is the pathway by which the stimulus giving rise to an unilateral convulsion spreads to the opposite hemisphere, but Franck and Unverricht found that section of the corpus callosum in animals plays no part in preventing a convulsion from becoming generalized.

Between 1900 and 1908, Liepmann published a series of brilliant papers in which he pointed out the predominant influence exerted in man by the left hemisphere, and the value of apraxia as a diagnostic sign of callosal damage. Certain functions of the limbs acquired by experience and practice and comparable to the functions of speech, have their cortical centres situated in the left hemisphere, these centres being connected with the corresponding centres in the right hemisphere by means of the anterior fibres of the corpus callosum. Apraxia may be purely motor, or it may be sensory in origin, due to failure of recognition of objects, just as agraphia is produced by visual agnosia of words.

Over 95 per cent. of people are right-handed. In them the left cerebral hemisphere is the dominant one, and besides controlling the limbs of the right side of the body, exercises a potent influence upon the right cerebral hemisphere by means of the commissural fibres of the corpus callosum. Thus, many movements of the left limbs are initiated through the corpus callosum by the left hemisphere, so that a left-sided brain lesion, if implicating callosal fibres, may produce not only a right-sided hemiplegia but also apraxia of the non-paralysed left side. This was the first serious contribution to the physiology of the motor functions of the corpus callosum.

According to Wilson [*Brain*, 1908] three clinical varieties of apraxia may be met with: (1) A *sensory* form of apraxia where the patient, when shown an object, is unable to use it in the correct fashion, because the idea in the patient's mind of the nature of the object is incorrect, i.e., there is visual agnosia. Thus, a person shown a pair of scissors and asked to use them may not recognize the scissors as such, and may perhaps convey them to his mouth as he would a fork. (2) An *ideational* type of apraxia where the patient recognizes objects, but through want of attention or defective retentiveness of memory is unable to execute the main idea of the movement. A man, shown a matchbox and a candle and asked to use them, may put the candle in his pocket and open the matchbox, recognizing and naming the objects, but unable to grasp and execute the main idea suggested to him, viz., to light the candle. (3) A *motor* type of apraxia, where objects shown are recognized and commands given are understood, yet the latter cannot be executed. Although the general idea of the action is understood and there is no paresis, the normally worked out idea cannot be exteriorized. Thus, an apraxic patient with a right hemiparesis, asked to make a military salute with his left hand, although comprehending what is needed of him and having no paralysis of his left upper limb, is unable to exteriorize the idea of the movement.

The excellent studies of Charles Foix and Pierre Hillemand on "Lesions of the Anterior Cerebral Artery" have done much to enlarge our knowledge of the functions of the corpus callosum and have given us a clear picture of callosal apraxia. The anterior cerebral artery supplies the anterior 7/8 of the corpus callosum by branches arising from the concavity of the callosal arterial arch. This artery supplies also the orbital lobule and the prefrontal lobe and all the medial aspect of the cortex except the occipital supply of the posterior cerebral artery. On the lateral aspect of the hemisphere it supplies the first frontal convolution, the superior part of the two Rolandic convolutions, and the parietal convolution near the inter-hemispherical fissure. Besides this, the artery supplies the centrum ovale in the neighbourhood of the caudate nucleus and the head of the caudate nucleus itself.

Cortical or subcortical lesions of this artery, associated with arterial obliteration of the anterior cerebral supply of the centrum ovale, produce monoplegia or hemiplegia with weakness predominating in the lower extremity. When, however, destruction of the callosal arterial supply occurs with softening of the anterior 7/8 of the corpus callosum, *left-sided motor apraxia* is added to the above syndrome. The apraxia is not met with unless there is softening of the corpus callosum, and the apraxic syndrome is always on the left side, irrespective of the side of the arterial lesion. These authors point out that this *left-sided, unilateral motor apraxia*, met with in callosal lesions, differs from the apraxia met with in lesions of other parts of the hemispheres. In lesions of the parietal and supra-marginal gyri the apraxia is bilateral and of the ideo-motor type, and is associated with right hemiplegia, aphasia, and perhaps also hemianopia and sensory loss. In lesions of the temporal lobe apraxia may also occur, but it is of the ideational type and associated with further psychical disturbances. These workers have thus established the distinction of callosal apraxia from other forms, and have shown the predominance of the left hemisphere in the normal eupraxia of movement.

La Fora and Prados performed an interesting series of experiments in 1921 on this subject. They trained a series of male cats and monkeys of both sexes to perform rather complicated movements requiring certain special movements of the left fore limb, while they reached for food with the right. After each animal was thoroughly trained its corpus callosum was cut. These workers had uncommonly bad fortune with their surgical results, and those animals which did survive seem apparently to have gone through such a stormy period of convalescence that the procedures taught had been forgotten. This approach, however, would seem a logical one, particularly if one employed the higher apes which are, according to Henschen and Kohley, predominantly right-handed.

Hartmann and Trendelenburg published a series of experiments of a somewhat comparable nature in 1927. Of the ten apes upon which they operated only four survived. In only one of these were they successful in performing a complete section of the corpus callosum. They found no evidence of apraxia in their animals.

The study of conditioned reflexes in animals by Pavlov and his co-workers has done more to clear our ideas regarding the functions of the corpus callosum. Bykoff has shown that in dogs a differentiation of the direction of a sound requires a united activity of both hemispheres. In normal dogs the differentiation of sounds by their direction presents no more difficulty than any other differentiation, and is capable of great precision. Salivary secretion reflexes conditioned by sound of a given pitch coming from a certain direction are easily established. If, however, the corpus callosum be sectioned and new conditioned alimentary reflexes established, the dog is unable to make any differentiation of the direction of the sound. "Other differentiations were obtained in this dog easily and rapidly, but never one involving localization of the source of the sound" (Anrep).

Tactile conditioned reflexes, which were developed from different places on one side of the body, reproduce themselves with surprising accuracy on symmetrical places of the other side of the body. Anrep demonstrated this both for positive and negative reflexes to tactile stimuli. Bykoff found that after section of the corpus callosum conditioned reflexes to tactile stimulation of the two sides became entirely independent of one another. We may also refer to the work of Anrep on "The Irradiation of Conditioned Reflexes" (*Proc. Roy. Soc.*, B, 93, 1923).

These experiments are of great importance in showing that the bilateral synergic activity of the hemispheres may be dependent on the corpus callosum, and indicating the part which the corpus callosum plays in the development of symmetrical reproduction of function in the hemispheres.

In conclusion, one may summarize the hypothesis of Mingazzini, formulated in his monograph, "Der Balken." In the anterior third of the corpus callosum (portio verbalis et praxica) run fibres connecting the motor speech centres, and aiding in the harmonious functioning of these areas (und zur Ergänzung der Sprachfunktion beitragen). The middle and part of the anterior third of the corpus callosum (portio praxica) contain fibres connecting the cortical areas for stereognosis, the measurement of muscular movements and certain forms of deep sensibility, the visual and auditory areas in both hemispheres, which make possible co-ordination and harmonious working of the limb movements, e.g., as in painting a picture or in playing a musical instrument. The posterior third (portio sensorialis), including the splenium, is of greatest size in man, a fact which is associated with the development of larger cortical centres for vision and hearing and their commissural connections. This posterior third contains fibres connecting these cortical areas with the motor and speech centres, making possible eupraxia of speech, voluntary action, mimicry, &c.

He supposes that the corpus callosum has a psychical function consisting in the association of ideas formed in the cortex of both hemispheres, and thus permitting of a harmonious combination of these ideas; and he states that the psychical disturbances arising from lesions of the corpus callosum are to be ascribed to an interruption of the co-ordinating pathways. This supposition is shared by Gand, Hitzig, and also by Cajal. There are, of course, cases where despite a lesion of the corpus callosum no psychical disturbance resulted, and Mingazzini explains this on the hypothesis that the lower commissural systems take over its function and substitute for it.

DISCREPANCIES BETWEEN PHYSIOLOGY AND THE KNOWN CLINICAL PICTURE OF PATHOLOGICAL LESIONS.

We see that whatever knowledge we possess of the physiology of the corpus callosum is partly hypothetical and the result of suppositions arising from anatomical findings. The results of clear-cut vascular lesions have contributed largely to our knowledge. Only in the recent experiments of Bykoff and Anrep has a purely physiological approach to the problem been made.

We may say unhesitatingly that the study of neoplasms of the corpus callosum will throw no light whatever on the physiology of that structure. Lesions produced by neoplasms differ in this respect from more clear-cut vascular lesions. There are grave discrepancies in the syndromes produced by tumours and those produced by experimental section of the callosal fibres. Every neuropathologist has observed the gross infiltration of nerve tracts by tumour tissue with the preservation of many microscopically intact fibres.

The lethargy and apathy of patients with callosal tumours have been produced in dogs, but these symptoms must be evaluated as they arise in animals which have been subjected to any mechanical cerebral interference. The quadriplegia, characteristic of the tumour syndrome in man, is not a marked feature after section of the corpus callosum in animals. Again, in vascular lesions producing softening of the corpus callosum there is no mention in recorded cases of any psychical change comparable to that which one associates with the tumour syndrome. In our study of neoplasms of this region of the brain we have been unable to confirm that apraxia is a frequent symptom. Some of our case records date back to a period before the publication of Liepmann's paper in 1907, and in some of the cases, admittedly, apraxia may have been present but obscured by the lethargic condition of the patient.

Taking into account the completeness of the case records, our series of tumour cases would lead us to believe that apraxia is not a common symptom of tumours of the corpus callosum.

The symptoms in corpus callosum tumours are largely of the "neighbourhood" type and arise from involvement of, or pressure on, adjacent structures by the growth.

REPORT OF FOURTEEN CASE HISTORIES.

In the 1893 edition of his textbook, Gowers states "the chief lesion that occurs in the corpus callosum is tumour, but this almost always extends into one or both hemispheres. Mental dullness and stupor, with weakness in the limbs, greater on one side, have been present in many cases, and in some there has been disturbance of speech and locomotion; but it is probable that these symptoms (with the possible exception of the mental dullness) are due to the pressure on, or extension into, the cerebral hemispheres. We do not yet know of any symptoms that are the result of the damage to the callosal fibres." In a footnote he refers to the four cases described by Bristowe in this Journal in 1884. Bristowe's paper was an attempt to emphasise the peculiar mental state, associated with progressive hemiparesis on the one side and "vague symptoms on the other," which characterizes these cases, and he attempted to stress other points, e.g., the absence of cranial nerve palsies and the paucity of general symptoms which might give a clue in making the diagnosis during life.

The fourteen cases which we are recording here have been carefully selected as being neoplasms apparently originating in, and largely confined to, the corpus callosum. Frontal tumours and occipital tumours extending into the corpus callosum, have been excluded. A study of these cases leads us to emphasize certain groups of symptoms which define with greater clearness the clinical picture of tumour of the corpus callosum.

(1) Hemiplegic weakness with pyramidal signs on the opposite side is frequent and early. Whereas great stress has been laid upon apraxia as a physical sign, it is not a prominent feature of our cases and is found probably in hardly more than 10 per cent.

(2) The mental changes which are so commonly present are often the first symptom. Apathy, drowsiness and defect of memory, are met with more commonly than in growths elsewhere, and occur with such regularity in the corpus callosum syndrome as to be characteristic.

(3) Epileptiform convulsions, in our series, are relatively frequent and attention may be drawn to the presence of other involuntary movements, tremor and choreiform movements, which are noted throughout our cases.

(4) The occurrence of yellow cerebrospinal fluid in four of the cases is, in our opinion, a point of considerable importance.

(5) In the main the general symptoms of cerebral tumour have been in abeyance, so that the diagnosis arrived at during life, in most of the cases here recorded, was that of cerebral vascular disease.

Gowers' statement that "the symptoms (with the possible exception of mental dullness) are due to pressure on to, or extension into, the cerebral hemispheres," we believe still holds. In the light of physiological work summarized in a previous part of this paper, we have little doubt that the early psychical changes exhibited by these patients are largely due to interruption of the association fibres in the corpus callosum.

I.—Cases illustrating Early Hemiplegia with Later Appearance of Pyramidal Signs on the Opposite Side.

Case 1 (*National Hospital, Queen Square, London*).—*Tumour in posterior two-thirds of corpus callosum. Fairly sudden onset with left hemiplegia and drowsiness. First seen in Out-Patient Department with bilateral pyramidal signs. Later, mental changes and increasing drowsiness. Pupils unequal. No papillœdema or vomiting. No apraxia. Yellow cerebrospinal fluid.*

Morris E., aged 61. Admitted under Dr. Stewart, September 19, 1919.

Two months before admission patient's wife noticed he had weakness of the left side although he had had no fit or loss of consciousness. Seen in the Outpatient Department by Dr. Grainger Stewart a week later the abdominal reflexes were absent, the tendon reflexes brisker on the left side than the right and both plantar responses extensor. The weakness of the left lower limb became progressively worse. His wife states that since his illness commenced he would fall off to sleep in the middle of a conversation.

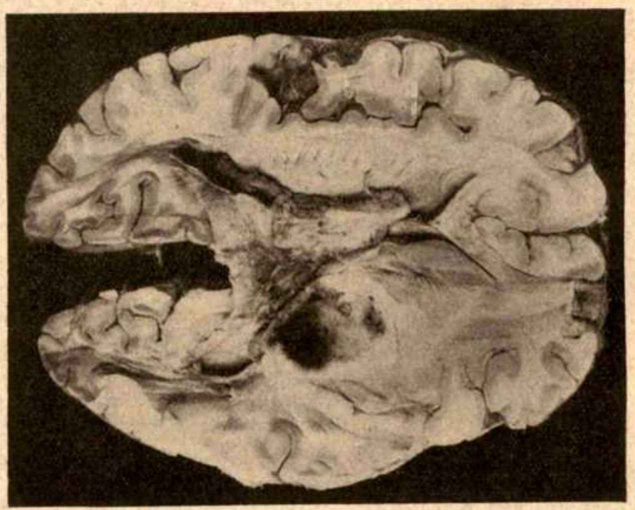


FIG. 1 (*Case* 1).—Tumour occupying the splenium of the corpus callosum and invading the right centrum ovale and fornix. The right lenticular nucleus is replaced by a solid mass of growth. The tumour surrounds the posterior horn of the right ventricle but does not invade it, and appears over a small part of the wall of the posterior horn of the left ventricle.

One week before admission he became "light-headed," more drowsy and apathetic and he constantly patted the right side of his head, although there had been no complaint of headache and no vomiting had occurred.

On admission the patient could be induced to answer questions and there was no aphasia or apraxia. The optic discs and fundi were normal; there was left-sided visual inattention. There was slight left hemiparesis with marked weakness of the left face on emotional movement. There was left hemianæsthesia to cotton-wool and pin prick, and the left corneal reflex was diminished. The tongue was protruded to the left. The abdominal reflexes were absent, the tendon reflexes of the arms brisker on the left than the right. The knee-jerks were brisk and equal and the ankle-jerks greater on the left side. Both plantar responses were extensor.

Later the patient became more drowsy and the left-sided weakness became more marked. The plantar responses were variable. The left pupil became much larger than the right and there was constant conjugate movement of the eyes to the right. A week later there was spastic weakness of the right upper limb and some head retraction.

Cerebrospinal fluid.—Yellowish with coagulum, contained 2 cells (large lymphocytes) per c.mm.; albumin, 0·06 per cent.: chlorides, 0.69 per cent.; good reduction of Fehling; Wassermann reaction negative.

October 11, 1919.—Right parieto-temporal decompression. The patient died three days later.

At autopsy a tumour was found occupying the splenium of the corpus callosum, extending into the right centrale ovale (see fig. 1).

This case was characterized by the ingravescent onset of left hemiparesis, with later absent abdominal reflexes and the appearance of an extensor plantar response in the right as well as the left foot. Drowsiness and apathy were early symptoms in spite of the absence of headache, vomiting and papillœdema. But for the condition of the cerebrospinal fluid, it is possible that he might have been regarded as a cerebral vascular lesion. The bilateral pyramidal signs appeared to be due simply to the median position of the growth, and the predominance on left side to an extension of the growth into the right centrum ovale. The dilatation of the left pupil, the conjugate movements of the eyes to the right and the head retraction, are worthy of note.

Case 2 (National Hospital, Queen Square, London).—Tumour of the middle and posterior thirds of the corpus callosum. For three weeks bouts of irritability. Gradual onset of right-sided weakness and tremor. Progressive defect of memory with perseveration and aphasia. No apraxia, although involvement of the middle of the corpus callosum. Headache, vomiting and papillœdema. Right visual inattention. Pupils unequal. Later, bilateral pyramidal signs. Yellow cerebrospinal fluid. Decompression.

James H., aged 53. Admitted under Dr. Taylor, September, 19, 1919.

Three weeks before admission patient complained of severe occipital headache, worst in the morning, and had one bout of vomiting. He became very irritable and gave up work. Ten days before admission he began to lose the use of the right arm and leg. The weakness of the arm was slight, and his wife observed that the limb was tremulous when he held a cup of tea. About this time his speech became indistinct. Six days before admission his memory began to fail, he could not remember the date, and this had become progressively worse. He had difficulty in choosing the right word and would, for instance, ask for a halfpenny when he wanted his pipe.

Patient, on admission, was quite conscious and lay in bed occasionally talking to himself. He was completely disoriented in space and time. His spontaneous speech was almost unintelligible, and he used jargon words, e.g., called soap "choif," but answered questions normally and executed spoken commands correctly but with a tendency to perseverate in his actions. Asked to repeat words and phrases, he again perseverated in his answers. He did not appear to comprehend written commands, and read print aloud only with difficulty. He gave no response when asked to write spontaneously and could not copy the word "James," but he wrote to dictation the word "petrol" in printed capitals in a tremulous hand; i.e., he was definitely aphasic, chiefly on the motor side, with perseveration of speech and actions, and probably some alexia. There was no apraxia—tested with matchbox, key and various other articles. The optic discs were swollen to four dioptres, with striate hæmorrhages in both eyes, and there was right-sided visual inattention. There was a slight right hemiparesis and a fine tremor of the outstretched right hand. The tendon reflexes were all brisker on the right side. The abdominal reflexes were absent on the right side, and the right plantar response was extensor. The left upper abdominal reflex was not elicited.

A week later the general intelligence became much more impaired, the left pupil was larger than the right and did not react to light or on accommodation. Both plantar responses were now extensor and the abdominal reflexes absent on two sides. There was marked general tremulousness, and he became incontinent of urine and fæces. A week later he became intensely drowsy, and a lumbar puncture was performed.

Cerebrospinal fluid.—Yellow fluid 10 cells per c.mm. (large and small lymphocytes); albumin 0·06 per cent.; chlorides 0·74 per cent.; reduced Fehling; Wassermann reaction negative.

A left temporo-frontal decompression was performed on October 3, 1919, by Mr. Armour. After this the plantar responses became flexor and the incontinence lessened, but the patient succumbed on October 14.

At the post-mortem a large tumour was found occupying the middle and the splenium of the corpus callosum and all the region of the left optic thalamus. The tumour invaded the posterior part of the lenticular nucleus and almost obliterated the left lateral ventricle, the middle portion and posterior horn of which it invaded.

In this case the presence of headache, vomiting and papillœdema made the diagnosis of cerebral tumour obvious. The yellow cerebrospinal fluid would suggest a proximity of the growth to the ventricles, and the bilateral pyramidal signs a median localization. The right visual inattention was probably due to an extension of the growth towards the left optic radiation, and the tremor due to extension towards the basal ganglia. This case, like the previous one, showed inequality of the pupils. The absence of apraxia, although the patient was right-handed and had a right hemiparesis, is noteworthy.

Case 3. (*National Hospital, Queen Square, London*).—*Tumour of the middle of the corpus callosum. Six months' history of gradually increasing lef hemiparesis, commencing in the leg, with loss of memory and apathy. Later left-sided Jacksonian attacks and quadriplegia.*

Rose M., aged 12. Admitted under Dr. Hughlings Jackson, April, 4, 1896; died April 18, 1896.

Until six months ago patient was bright and merry. Gradual languor began to overtake her, with some dragging of the left leg. Three months later the left upper limb became paralysed, and by this time she was said to have become stupid and had no memory.

She was admitted comatose after a left-sided fit the previous day. Fourteen days before admission she began to suffer from vertical headaches and vomiting

On examination the patient was fairly well nourished, comatose, with slight bilateral proptosis. She could just be roused by shouting. Both optic discs were swollen to the extent of one dioptre. The left pupil was larger than the right and both pupils dilated when a beam of light was directed towards them. There were slow lateral movements of the eyes—no facial asymmetry. Both upper and lower limbs were flaccid and extended, and it was noticed that the weakness was greater on the left side. The knee-jerks could not be elicited; the plantar responses were absent. There was incontinence of urine and fæces.

Fourteen days after admission patient died, and at autopsy a degenerating tumour was found occupying the middle of the corpus callosum.

In cases where all four limbs are involved, paralysis is usually of the flaccid type. Case 1 is an exception. It is interesting to note that in the case recorded above, as well as in the two previous cases, the pupils were unequal. In this case Jacksonian convulsions occurred.

Case 4 (*National Hospital, Queen Square, London*).—*Tumour of splenium. Fairly sudden onset with progressive agraphia and right-sided weakness. Progressive memory defect and drowsiness. No apraxia. Inconstant coarse tremor of the trunk and lower limbs.*

Henry L., aged 62. Admitted under Dr. Holmes, September 24, 1925.

Three weeks before admission patient's sister noticed that his letters to her were incoherent; words were left out and he omitted letters in spelling words. His handwriting was becoming illegible. She went to the Isle of Wight, where he was staying, and found that he had developed some weakness of the right arm and leg. She was struck by his slowness of thought and utterance, his loss of memory and his drowsiness. He could express himself with a little help, and he was still able to dress himself and perform the necessary daily offices of attending to his wants.

Although drowsy during the day, he was kept awake at times during the night by violent vertical headache which had come on two days previously. No vomiting. He was a healthy and vigorous man and until recently used to follow the hounds on foot.

On admission patient was semi-comatose. He could be roused with difficulty but did not comprehend questions or commands. His answers were monosyllabic and practically unintelligible. The right hand lay limply at the side and fell with a thud when raised and allowed to drop. There was slight right facial weakness. Occasionally a sort of shuddering tremor spread over the body. The respirations were periodic.

The patient was obviously aphasic; there had been no apraxia and no fits. Both fundi showed arteriosclerotic changes in the vessels, with blurring of the disc margins but no definite swelling. There was an inconstant coarse tremor of the trunk and proximal parts of the lower limbs. All the tendon reflexes were elicited more briskly on the right than on the left; the right plantar response was extensor, and all the abdominal reflexes absent. The patient was incontinent of urine and fæces. The blood-pressure was 158/98 mm. Hg; the second aortic sound was accentuated and hollow.

The blood-urea was found to be 57 mg. per 100 c.c. There was no albuminuria. The urea concentration test gave normal results. The Wassermann reaction in the blood was negative.

Patient died on October 16, 1925, twenty-two days after admission. At autopsy a tumour was found occupying the splenium of the corpus callosum.

The similarity of the clinical picture in this case to that of cerebral arteriosclerosis is striking. The rapid progress of the symptoms and the relatively slight arteriosclerosis visibly present, with the occurrence of bilateral pyramidal signs and bouts of coarse tremor in the upper and lower limbs, suggested a median neoplasm.

In the hemiparesis of corpus callosum tumours, Steinert has noted a predominance of weakness in the lower limb. This is confirmed by our experience. In most of the cases here recorded the weakness affected first one side, chiefly in the leg, and later spread to the lower limb of the opposite side. Paraplegia was not observed.

II.—*Cases illustrating Early Psychical Changes.*

Psychical changes of a particular kind are the most characteristic feature of our group of tumours of the corpus callosum. Their extreme frequency has been emphasized by other authors. In 110 cases collected by Mingazzini, they were absent only in 8; of 116 cases collected by Balduzzi, they were absent only in 10. They commence early and progress rapidly, and a condition is soon reached in which the mental changes dominate the clinical picture. The early stages are characterized by poverty of movement and thought, with lack of spontaneity. Torpor, apathy and depression, with loss of memory, characterize the early stages. Later, hallucinations may arise, the patient becomes disoriented, indifferent to his surroundings and to emotion. The last stages are characterized by dementia, interrupted by periods of transient motor excitement. The variability in the mental state from day to day is well recognized in the literature. We are in agreement with Stern, who believes that psychical changes are infinitely commoner in tumours of the corpus callosum than in tumours in other regions of the brain. The psychical changes may occur at a stage when there is very little increase of intracranial pressure. In the later stages, the mental symptoms due to involvement of the corpus callosum are difficult to separate from those due to increase of intracranial pressure.

Case 5 (*National Hospital, Queen Square, London*).—*Tumour of the splenium. Gradual onset with general debility of twelve months' duration. Uncinate fits. Signs of increased intracranial pressure. Gross memory defect for recent events. Disorientation. Statuesque gait and tremor of the right upper limb; bilateral pyramidal signs. Yellow cerebrospinal fluid with increase in albumin and cell count.*

Marian H., aged 46. Admitted under Dr. Collier, February 20, 1922. One year ago patient began to show signs of fatigue, apathy and depression. She complained frequently of bad tastes in her mouth, and for a few days before admission she complained of feeling "a horrible smell" in her nostrils at times. Five weeks before admission she complained of frontal headache and her husband noticed a failure of memory which lasted only a few days.

Seven days before admission her memory again failed; speaking to her husband she would say "Where is my husband? Oh! are you Fred?" The right upper limb began to shake and three days before admission she vomited. The patient was previously a healthy woman.

On examination, there was great failure of memory, especially for recent events, and she could give no account whatever of her illness. She was disoriented in space and time and could not tell how many days she had been in hospital, although she had arrived that afternoon. She could not remember who had brought her and could not tell what day of the week it was. She could not tell her name, her age, or the number of the house in which she lived, although with difficulty she remembered the year of her birth and the name of the street she lived in. She stated that she had had no vomiting although she had had a severe attack three days before, which she had apparently forgotten.

She showed a tendency to repeat phrases or remarks during the examination and complained of feeling exhausted. The expression was vacant and abstracted.

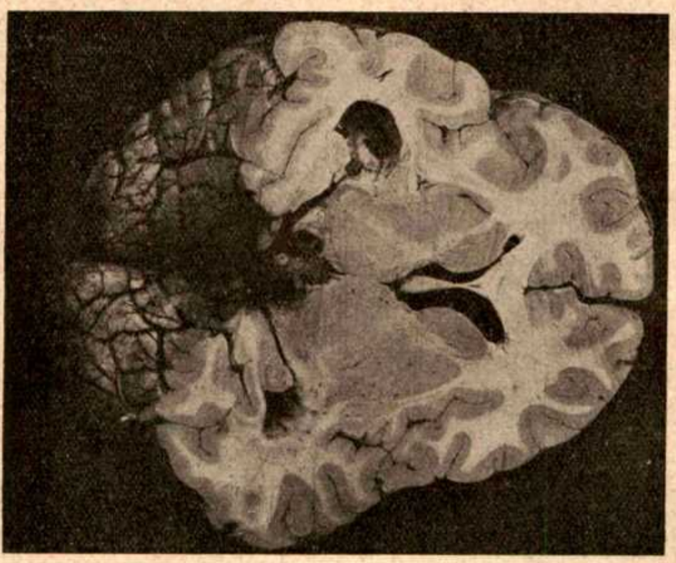


FIG. 2 (*Case* 5).—Sarcoma occupying the posterior part of the corpus callosum and extending on either side of this, widely separating the posterior horns of the lateral ventricles. Exposed from above.

R. V. $\frac{6}{18}$, L. V. $\frac{6}{12}$. Fields of vision showed left visual inattention. Both the discs showed papillœdema, R.O.D. + 2, L.O.D. + 2, retinal veins tortuous. The right pupil was larger than the left. Both pupils reacted to light and on accommodation. The other cranial nerves were normal.

Both hand-grips were equally feeble. The right upper limb showed a tremor of fairly wide range, rhythmic and slow, seen when the arms were outstretched. With the finger-nose test the tremor was intensified towards the end of the movement. There was no sensory defect and no change in the tendon reflexes. The upper and lower abdominal reflexes were absent; the plantar responses flexor in type. The gait was statuesque and the patient leaned slightly backwards. There was slight general rigidity and the head was held tilted to the left. Patient did not swing the arms in walking, and the right upper limb was held slightly in front.

Ten days later both plantar responses were extensor. Dr. Collier saw this patient on March 5, 1922, and was of the opinion that the tremor was a spontaneous movement produced by pressure on, or lesion in, the left posterior lenticular nucleus, and that the loss of memory was due to a tumour of the splenium.

The cerebrospinal fluid was slightly yellow. There were 66 cells per c.mm. (mononuclears and polymorphs). The amount of total protein was 0·07 per cent. Nonne-Apelt positive. Lange, 0001110000.

Operation March 7, 1922 (Mr. Sargent). A left parieto-temporal craniotomy was performed. There was little increase in intracranial pressure. A probe was inserted into the middle temporal gyrus in a slightly upward direction and met with resistance at the depth of about an inch. An incision was then made in the posterior part of the middle temporal gyrus, but no growth could be discovered.

At autopsy, horizontal section of the brain at the level of the superior fibres of the corpus callosum showed a tumour occupying the posterior third of the corpus callosum and extending on either side of this, 4 cms. into the right hemisphere and 4·5 cms. into the left, in the direction of the biceps major. The growth was symmetrical and heart-shaped (apex forwards) extending towards the optic thalamus and pushing into, but not invading, the posterior horns of both lateral ventricles. The two halves of the choroid plexus were widely separated by the growth and lay in close apposition to the lateral walls of the body of the ventricles. The anterior horn of the ventricles showed no distension. The tumour extended for the most part posteriorly and laterally to the corpus striatum in the direction of the optic radiation. (See fig. 2.)

This case is a beautiful example of a tumour of the splenium diagnosed during life, illustrating the early onset of apathy and depression long before the onset of signs in the limbs. The failure of memory for recent events led to the patient's statement that she had had no vomiting, although she had had a severe attack three days previously.

Dr. James Collier has seen a case in which the patient was crying out with severe headache and holding his head, and when seen ten minutes later, when the headache had passed off, had apparently completely forgotten and emphatically denied having suffered from headache during his illness. Many authors have commented on the vacant and abstracted facial expression of these cases.

Besides the characteristic mental picture, this case also exhibited bilateral pyramidal signs, fits, tremors, inequality of the pupils and yellow cerebrospinal fluid, as in the majority of our cases.

The two following cases showed early depression and apathy.

Case 6 (National Hospital, Queen Square, London).—Tumour of the anterior and middle thirds of the corpus callosum, causing distortion of the anterior horn of right ventricle. Four months' history of general weakness, depression and apathy. Three months ago patient had a fit, which was followed by a progressive left hemiparesis. Dull on admission, with gross swelling of both optic discs. Left attentional hemianopia. Bilateral pyramidal signs. Static tremor of right upper limb. Yellow cerebrospinal fluid.

Edward M., aged 49. Admitted under Dr. Holmes, May 17, 1926. The patient was well until three months before admission, when he began to have "fainting attacks," which sometimes caused him to fall down. These attacks were followed by vacantness and disorientation lasting several hours, and it was noticed that between his attacks he had become depressed and mentally much duller.

The fainting attacks continued, and in these his left arm and leg would sometimes shake. He had one severe attack of vomiting and two generalized epileptiform convulsions. He complained of frequent severe headaches and blamed these for the recent loss of memory which had been noticed by his friends.

One month before admission he began to lose the use of his left arm and leg, and his speech was occasionally incoherent. This left-sided weakness had been becoming progressively worse.

On examination, the patient was extremely apathetic and mentally slow. It was impossible to elicit any history from the patient himself, as he could not remember the details of his illness. The speech was slow but there was no aphasia. The optic discs showed tortuosity of the arteries with increase of central light reflex. The outline of the discs was clear and they were of good colour. The pupils were equal and reacted normally. The external ocular movements were full but convergence was not sustained. There was marked left lower facial weakness, more on voluntary than emotional movement. The tongue, when protruded, deviated slightly to the left. There was almost complete left hemiparesis, the lower limb being completely paralysed, the upper limb preserving only feeble finger movements. The left lower limb was flaccid, the tone of the left arm slightly increased. There was no sensory loss. All the tendon reflexes were brisker on the left side. The left upper and lower abdominal reflexes were absent. The left plantar was extensor, with a marked withdrawal reflex.

The patient became much more drowsy, with incontinence at times. At one period, for twelve hours, he had intermittent twitching of the right face and upper limb. It was noticed that he lacked spontaneity. He would not speak or move unless commanded. There was fairly frequent static tremor, coarse and rapid in the right upper limb, and he developed left-sided attention hemianopia. It was noted that "the patient scarcely makes any spontaneous utterance, his face is blank, sunken and drawn."

The cerebrospinal fluid was yellowish, containing eight cells per c.mm. and

0·3 per cent of albumin. The Nonne-Apelt test was positive; Pandy test positive; Lange curve 0000011221. The Wassermann reaction was negative in the cerebrospinal fluid and blood. The cerebrospinal fluid contained 62 mg. per cent of urea.

Before death the patient developed slight swelling of both optic discs, in the right eye + 4 D. and in the left eye + 1½ D. The systolic blood-pressure measured from 145 to 132 mm. of mercury; the diastolic was 90 mm.

At autopsy a tumour was found attached to the falx cerebri infiltrating the corpus callosum about its centre and embedded in the right callosal convolution. The left callosal convolution was compressed but not invaded. The tumour readily separated from the brain tissue, revealing considerable destruction of the corpus callosum and the right callosal convolution.

Case 7 (Johns Hopkins Hospital, Baltimore).—Tumour of anterior two-thirds of corpus callosum. Seven months' history of apathy and dullness, poverty of ideas and slowness of thought. Later, headache, with stiffness of the neck, vomiting, giddiness and diplopia. Right peripheral facial palsy. Tendency to fall forwards.

Bessie M., aged 37. Admitted under Dr. Dandy, February 2, 1926. Died, February 24, 1926.

The patient attended the Johns Hopkins Dispensary on February 1, and at this time it was ascertained from her sister that for seven months she had been dull and apathetic, with poverty of ideas and slowness of thought. During this time the patient had begun to suffer from occipital headaches and double vision. In her sister's words, "She cannot seem to think right and is slow in performing her duties around the house." For some time she had had a staggering gait, and when she fell it was almost always forwards on her face. Five months before she had complained of "pins and needles" in both upper limbs.

About three months before admission, she had a period of marked improvement which lasted for some weeks. Her headaches again became worse, she frequently vomited, and for three or four days prior to her admission she was incontinent of urine.

On admission to the hospital the next day, she was found to have bilateral papillœdema and a right peripheral seventh nerve palsy. There was no evidence of involvement of the pyramidal tracts.

Ventriculography was performed and the fluid withdrawn was blood-stained. X-ray pictures, after injecting the ventricles with air, demonstrated clearly a mid-line tumour lying anteriorly. Three days later, Dr. Dandy performed an operation but found an inoperable glioma, and three weeks later the patient died.

At autopsy, a vascular tumour about 2 cm. in diameter was found occupying the anterior two-thirds of the corpus callosum, extending towards the internal capsule and the optic thalamus on the left side. The ventricles were not dilated, but the anterior horns were largely occupied by a greyish tumour mass growing from the corpus callosum and measuring 4 cm. in transverse diameter and from 2 to 3 cm. vertically. The fornix lay on its lower surface. This growth involved the genu and reached into the superior longitudinal fissure. A small tumour mass occupied the anterior part of the left caudate nucleus.

Here the psychical changes appeared early, when somatic disturbances were slight, and some months before increase of intracranial pressure was evident. Incontinence is a symptom in this and in the following case and we connect it with the psychical condition. The tendency of this patient to fall forwards is worth noting. In a large tumour of this kind it is probably due to backward pressure on the vermis of the cerebellum. A study of cases of corpus callosum tumours in the literature in which this has occurred leads one to the conclusion that it is most commonly met with in tumours of the splenium.

The value of ventriculography in localizing these tumours is well illustrated in the above case.

Case 8 (*Johns Hopkins Hospital, Baltimore*).—*Tumour of the splenium. Early marked psychical changes, forgetfulness,* "*holes in the memory*"; *later, mental confusion. Four months' vomiting, headache and papillœdema. Diminution of sensibility over the left half of the body. Absence of abdominal reflexes on the left side.*

Claud W., aged 50. Admitted under Dr. Dandy on June 25, 1922. Died, July 12, 1922.

The patient's earliest symptoms were inability to remember and to think clearly, and drowsiness. Some months later his memory had become so bad that he could not remember what had been said to him or statements made by himself a few minutes before. For three months previous to his admission he had suffered from frontal headaches, dimness of vision, and a month before admission from vomiting.

On examination bilateral papillœdema was found. The pupils were equal, irregular in outline and reacted sluggishly to light. The visual fields could not be tested owing to the patient's mental state, but on several occasions he stated that he had constant dimness of vision and said he felt as though there was a film over his eyes. There was some sensory loss to cotton wool and pin prick over the entire left half of the body and the abdominal reflexes were absent on the left side. The plantar reflexes were flexor. The Wassermann reaction was negative.

The patient died after decompression, and at autopsy a tumour was found growing from the splenium 2 cm. in transverse diameter, compressing the posterior horn of the right lateral ventricle and extending into the occipital lobe and the optic thalamus on the right side. The fibres of the fornix were entirely replaced by the growth, which also involved the pineal gland. The pyramidal tracts appeared to have entirely escaped injury.

As in Case 5, and Dr. Collier's case, marked failure of memory for recent events led to difficulties in examination and discrepancies in the patient's statements. The psychical changes occurred many months before the onset of signs in the limbs. The drowsiness was probably due to encroachment of the growth on the third ventricle. The pineal gland and the roof of the third ventricle were found to have been destroyed by the neoplasm.

Case 9 (*National Hospital, Queen Square, London*).—*Tumour of the anterior two-thirds of the corpus callosum. Three months' history of mental changes, drowsiness and incontinence. Choreiform movements in the right upper and lower limbs followed by right-sided weakness, and later, bilateral pyramidal signs and quadriplegia. Cerebrospinal fluid clear.*

Frances C., aged 37. Admitted under Dr. Buzzard, May 28, 1919. Died, June 7.

The patient was a Pole and could speak very little English. Three months before admission she began to suffer from intense headache and depression. Two months before admission she took to her bed and since then frequently had incontinence and mental confusion. One month before admission her family noticed jerking and writhing movements in the right upper limb.

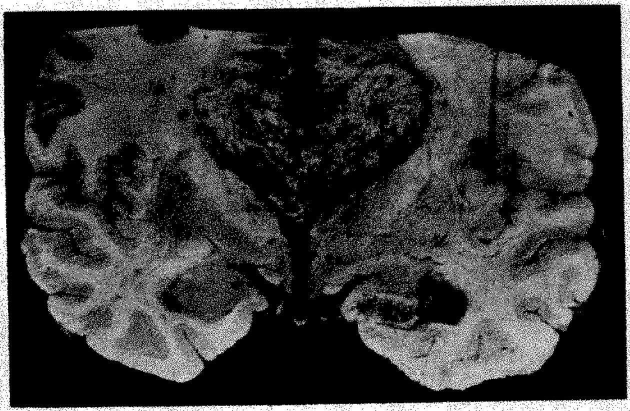


FIG. 3 (*Case* 9).—Coronal section of the brain through the third ventricle to show tumour occupying the body of the corpus callosum, invading the fornix and the lateral ventricles.

On examination the patient was a well-nourished woman, who could be roused to answer questions. Marked echolalia—when told to say "No," she would say "Say no;" and when told to say "Yes," she replied "Say yes." When disturbed there were intense choreiform movements in the limbs and face, more marked on the right side, and there was an exaggerated restlessness and fidgetiness in trying to make her grip or perform an action. Both plantar responses were extensor. The patient dropped off to sleep during the examination. The optic discs appeared normal.

One week later the choreiform movements had ceased and the patient was more comatose. A right hemiparesis gradually developed. Two days later the left leg had become paralysed and flaccid, and two days later all four limbs were powerless and slightly spastic.

The cerebrospinal fluid was clear, contained 0·04 per cent. of albumin; there were no cells and no excess of globulin. The Wassermann reaction was negative in blood and cerebrospinal fluid.

At autopsy a large tumour was found occupying the genu and anterior two-thirds of the corpus callosum (see fig. 3).

There is little doubt that the incontinence of these patients is of the mental type and is due to defect of attention and apathy. A considerable proportion of cases in the literature have shown drowsiness, an irresistible tendency to sleep and increasing obesity. It is probable that in these cases these symptoms are due to encroachment of the growth on the third ventricle and infundibulum. The descriptions by various authors of the psychical changes are remarkably alike; thus, Bristowe talks of "a stuporous condition, with lethargy and slowness of speech"; Ransom, of "increasing stupor with later hallucinations and bouts of irritability"; Schüpfer, of "lethargy and apathy"; Bruns, of "mental confusion, incontinence and great mental failure in the absence of any marked physical signs." It is to Raymond that we owe our first clear description of these psychical changes. He is the first of the earlier authors to contrast the psychical disturbances of brain tumours generally with those of the corpus callosum. Raymond stressed the early appearance of: (1) Changes in character; (2) dissociation of ideas and lack of continuity in thought; (3) eccentricity of conduct; (4) disturbance of memory, especially for recent events—"holes" in the memory; and (5) grave changes in character and variability of temperament.

This syndrome, to have localizing value, must appear early and in the absence of other somatic disturbances. We agree that this syndrome appears to be the one which is most frequently present in whole or part, but care must be taken to separate changes which may be due to general increase of intracranial pressure. In our experience the disease picture most commonly arises with a depressive condition.

An extremely comprehensive account of the psychical changes in tumours of the corpus callosum has recently been published by Egas Moniz, of Lisbon. The first of his cases, in the absence of all signs of increased intracranial pressure, showed marked psychical changes. The patient was drowsy but far from being apathetic. He showed diminution of intelligence, memory defect and poverty of ideation. There was deterioration of the moral sense, coprolalia, and loss of interest in his family and friends, recalling the picture of dementia præcox.

This author relates the type of mental change to the age of the patient. He states that in the young a syndrome recalling dementia præcox is common; in middle life the psychical changes simulate those of general paralysis, and in the aged those of senile dementia.

Every psychosis, however, may be simulated, especially the manic-depressive and dementia paralytica. Cases with paranoid symptoms and Korsakoff's psychosis are to be found in the literature. In Levy-Valensi's cases 57 showed apathy or emotional indifference; 17 defect of memory for recent events, sometimes simulating a Korsakoff state; 14 an irresistible tendency to sleep; 7 were disoriented, with a confusional state; 6 had bouts simulating mania, and 3 were definitely melancholic; 4 cases had hallucinations, and 2 delusions of persecution.

III.—*Cases illustrating Early Onset of Epileptiform Convulsions.*

In the cases already recorded fits have occurred during the course of the illness. In Case 3, Jacksonian attacks were noticed on the side in which the weakness was most marked. In Case 5 uncinate fits were observed early in the disease, and in Case 6 the epileptiform convulsions were generalized. In Cases 10 and 11, recorded below, generalized epileptiform convulsions were the earliest symptom and preceded the onset of mental changes and motor weakness, in the first case by six years and in the second case by four years.

Case 10 (*National Hospital, Queen Square, London*).—*Tumour of the genu and forceps anterior. Six years' history of epileptiform convulsions with occasional headache and vomiting, the left pupil enlarging during the attacks. Two months' history of drowsiness, slowness and apathy. Bilateral papillœdema, and later slight left-sided pyramidal signs.*

Stanley A., aged 33. Admitted under Dr. Buzzard, November 5, 1920.

Six years before admission the patient began to suffer from attacks in which he fell suddenly unconscious on his face on the floor. His sister stated that there was no rigidity or jerking of his limbs during the attacks, and that they lasted from ten to fifteen minutes. The attacks were always followed by vomiting and severe vertical headache. There were long intervals between his attacks. In the six years he had had perhaps seven altogether. Two months before admission, having been for a year free from fits, he noticed double vision for distant objects.

On examination he was a stout, fresh-complexioned man. Cerebration was notably slow and there was extreme lethargy, the patient dropping off to sleep constantly during the examination. His attention was poor; at times he was semi-comatose and roused only with difficulty. When roused he appeared intelligent and a good witness, though his reaction time was prolonged. There was great apathy and disinclination to be bothered with the fatigue of examination. His speech, when obtained, was normal, and there was no apraxia. The patient gave inaccurate replies to smelling tests.

Visual acuity in both eyes was $\frac{6}{18}$. The fields were full to rough testing. Papillœdema measured four dioptres in the right disc and five dioptres in the left. The surfaces of the discs exhibited a greyish speckled appearance, there were no hæmorrhages and no macular disturbance. Convergence was poor, especially of the left eye, and there was weakness of the right external rectus with fine nystagmus of the left eye on looking to the extreme right. Taste was normal on the tongue; there was marked tremor of the protruded tongue. There was slight weakness of the left lower face on voluntary and emotional movement.

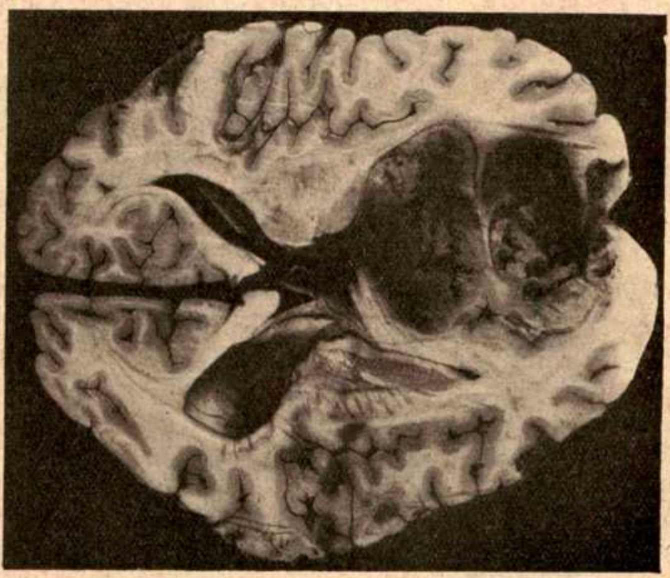


FIG. 4 (*Case* 10).—Sarcoma of the genu of the corpus callosum, exposed from above. This extremely vascular and hæmorrhagic growth had produced internal hydrocephalus by obstruction of the foramina of Monro.

A detailed examination of the motor system revealed no weakness, ataxia, or involuntary movement. Tone was slightly diminished in the left arm and leg. All the arm-jerks were absent; the knee-jerks were sluggish; the left ankle-jerk was brisker than the right; the right plantar was flexor, the left definitely extensor; the abdominal reflexes could not be elicited on the left side. There was no sphincter disturbance.

Four days after admission the patient was seen in an attack; the right pupil was smaller than the left; the left arm was extended and pronated, and there was opisthotonos. Patient had several fits after this, in all of them the left upper limb assuming the same position, the right pupil being smaller than the left.

That evening a right-sided decompression was performed. Five hours later the patient died.

At autopsy, a large tumour was found occupying the genu of the corpus callosum in the region of the forceps anterior. There was an area of thrombosis and softening in the distribution of the left anterior cerebral artery. The growth had extended into the right lateral ventricle and there was considerable dilatation of the posterior and descending horns, with compression of the right internal capsule (see fig. 4).

Case 11 (*National Hospital, Queen Square, London*).—*Tumour of splenium, invading the right optic thalamus. Four years' history of epileptiform convulsions with visual auræ. One month ago onset of mental change—apathy and impairment of memory for recent and remote events. Great lethargy, and later, delusions of persecution. Bilateral papillœdema. Palilalia. Unequal pupils and double vision. Slight progressive left-sided weakness with sensory loss. Sudden death after a severe attack of headache.*

Elizabeth H., aged 37. Admitted under Dr. Buzzard, August 10, 1894.

Four years ago the patient began to suffer from epileptic fits. She stated that her attacks were preceded by a sudden flash of bright light, or a sensation of darkness that seemed to come over her from the left side of her head. This was accompanied by a sensation of "fearful dread." An eye-witness stated that she gave two screams—the first, a scream of "It is coming"—the second, a hollow cry, coincident with her fall and loss of consciousness.

In the attack the head and eyes turned to the left, and later there was bilateral jerking of the limbs. On regaining her senses the patient moaned greatly as if in pain, and if spoken to would go off again into another convulsion. After the attack patient was said to be dazed and to suffer from headache. During the attack patient usually bit her tongue. There was no history of automatic acts following the seizures.

At first she used to have several attacks each day. Afterwards the fits occurred about once a week. Before each fit she was conscious of a light revolving on the left side and everything around becoming quite dark. Sometimes she was conscious of what looked like the shadow of a person on her left side, but this feeling was never followed by convulsion.

One month before admission patient had a very severe attack, and after that her brother noticed extreme lethargy day and night, great apathy and memory defect. Her speech, too, had become slower. Patient herself stated that occasionally she saw double.

The patient gave a history of previous good health. The catamenia had always been regular. The family history showed that one sister suffered from fits, an uncle had committed suicide and an aunt had died in an asylum. Her mother and one sister had suffered from consumption.

On examination the patient was a well-nourished woman of good colour. Her facial expression was placid, almost vacant, and cerebration seemed slowed down to a remarkable extent. She seemed to have lost interest in everything and wished only to be left alone, untroubled. Her memory was impaired for recent and remote events. She could not remember where she was, and thought that she was going to be ill and treated in some way. She did not recognize her relatives and was constantly dropping off to sleep. Her speech was slow and sibilant, and she frequently repeated words and syllables. She never complained of severe headache. Vision in the right eye was $\frac{6}{18}$ and in the left eye $\frac{6}{12}$. Both optic discs were blurred with three dioptres of swelling in the right disc and five dioptres of swelling in the left disc. There were no retinal hæmorrhages. The fields of vision were full to rough testing.

A detailed examination of taste and smell revealed no defect of smell but a general blunting of taste. The right pupil was smaller than the left and there was slight left lower facial weakness. There was no motor weakness of the limbs; the tendon reflexes were brisk and equal; the upper and lower abdominal reflexes were brisk, and there was no incontinence. Some blunting to cotton-wool and pin prick was noticed on the left side of the trunk, limbs, and face, and sense of position was impaired in the fingers of the left hand.

Three months later the patient's mental state continued to deteriorate. She was continually getting out of bed, resisting, and talking about plots against her, asking often for a policeman or a clergyman. She accused the house physician of being a great villain who plotted against her, and did not recognize either her doctor or her nurses. She took a long time to comprehend what was said to her.

Later, the patient became mentally clear and the swelling of her discs subsided. Two months later she again became dull mentally, lethargic and apathetic. Delusions of persecution again became evident. She thought that her food was being poisoned, and again that she was in an asylum. There was no apraxia or aphasia. The drowsiness increased and slight left-sided weakness became evident The temperature rose to 102° F., and she developed a basal pneumonia, from which she recovered.

Ten months after admission the patient was getting up for some hours each day, showing definite left-sided weakness. Fourteen months after admission she died suddenly after a severe attack of headache.

At autopsy a tumour of the splenium was found, invading the right optic thalamus.

The visual auræ in this case would appear to be due to the extension of the growth towards the occipital cortex. The psychical changes are worthy of note. In the early stages drowsiness and vacant expression were observed, with slowness of thought, speech, and action. This is the only one of our cases in which definite delusions of persecution arose. The remissions in the mental state, which were first emphasized by Ransom, are typified in the later history of this patient.

Case 12 (*Johns Hopkins Hospital, Baltimore*).—*Tumour of posterior two-thirds of corpus callosum. Fractured skull seven months before admission. Since then frequent epileptiform convulsions. Drowsiness, failure of memory and apathy. Admitted comatose. Slight left hemiplegic weakness.*

James B., aged 59. Admitted under Dr. Dandy January 21, 1927. Died January 30.

Seven months before admission patient was hit on the head by a falling tree and sustained a fractured skull, but was able after a week to return to his farm work. After this accident he suffered from frequent generalized epileptiform convulsions, and it was noticed that his mentality was becoming duller, his memory more defective, and slowness and poverty of thought became marked. Three weeks before admission he went to bed with headaches and drowsiness.

On examination there was slight left hemiplegic weakness. The fundi were normal. The day after admission ventricular puncture was performed, and showed that both lateral ventricles were dilated. Ventriculography showed the dilatation mostly in the anterior horn of the right ventricle. The skull showed evidences of old fracture.

At autopsy the ventricles were found to be dilated and to contain blood-stained fluid and clot. A soft, gelatinous tumour grew from the middle and posterior third of the corpus callosum into the ventricles, destroying the body of the corpus callosum and the splenium.

It is worthy of mention that in this case and in Case 14 there is a history of fracture of the skull. It is commonly taught that trauma plays no rôle in production of gliomata, but Cushing has suggested that it may do so in sarcomata and endotheliomata. A history of head injury is relatively frequently obtained in patients with cerebral tumour, and the explanation of it may be that the impairment of mental alertness, as the result of the growth, renders the patient incapable of avoiding accidents.

Case 13 (*National Hospital, Queen Square, London*).—*Tumour of the middle of the corpus callosum and the right island of Reil. Gradual onset of right hemiparesis, weakness spreading to the left side, with memory defect, slowness of cerebration and depression. Fits. Tremor of left arm and leg. Pleocytosis of* 79 *cells per c.mm. in the cerebrospinal fluid.*

William T., aged 52. Admitted under Dr. Taylor, August 24, 1919.

Five weeks before admission the patient, who was left-handed, began to have "faints" at his work, and his wife noticed the gradual onset of weakness and shaking in the right arm and leg. The right-sided weakness became progressively worse, and six days before admission the left arm and leg began to be similarly affected. During the eight days preceding his admission to hospital, the patient had three epileptiform convulsions with loss of consciousness, each lasting only a few minutes. He complained, on admission, of severe frontal headache.

On examination the patient was apathetic and slow of speech and cerebration, but there was no aphasia. He complained that "his memory had gone" and that he felt intensely depressed. Both optic discs were blurred but there was no appreciable swelling.

On testing with cotton-wool and pin prick the patient missed occasional touches on the right half of the trunk and right limbs, and in the right upper limb there was considerable loss of the sense of position. There was weakness of both upper limbs, greater in the right. The right lower limb was flaccid and feeble, voluntary power remained only in the quadriceps and adductors. The tendon reflexes were elicited briskly. The knee-jerks were brisker on the right side than on the left. Right ankle clonus was present. The right plantar response was extensor, the left flexor and the abdominal reflexes were absent on the right side and present on the left.

One week later the patient, although conscious, stated that he felt dazed and depressed. An occasional tremor was seen in the left upper and lower limbs. Both plantar responses were definitely extensor.

Cerebrospinal fluid.—Clear, colourless, 79 cells per c.mm., large and small mononuclears and phagocytes; albumin 0·05 per cent; chlorides 0·73 per cent; good reduction of Fehling; Wassermann reaction negative.

The temperature rose to 105° F., and the patient became comatose and died on September 5, 1919.

At autopsy a tumour was found occupying the middle of the corpus callosum and running outwards on the right side to the island of Reil.

In this case the attacks were simple, slight losses of consciousness, without convulsions. Here again, but for the result of the examination of the cerebrospinal fluid, a diagnosis of cerebral arteriosclerosis might be made.

IV.—*Tremor and Choreiform Movements.*

Cases 2, 4, 5, 6, and 13 presented tremor or tremulousness in one or more limbs. Case 9 had a right hemichorea. In Case 5 a tremor of the right upper limb was associated with a statuesque gait, rigidity and Parkinsonian attitude. This has been noted also by Guillain in a case published in the *Annales de Médecine,* in 1922, and by Bristowe in one of his four cases published in 1884. As in Case 6 of our series, a pyramidal hemiplegia on the one side may be associated with tremor in the contralateral limbs. Fourteen of Lévy-Valensi's cases had involuntary movements. In eleven of these cases there was true rhythmic "tremblement," in two cases there were choreiform movements, and in one case successive clonic jerkings of all four limbs.

V.—*Cerebrospinal Fluid.*

In seven of our cases an examination of the cerebro-spinal fluid was made, and in two the ventricular fluid was examined. In three of these cases only were the findings entirely negative. Four of the cases showed xanthochromia, increase of total protein (0·06 to 0·3 per cent.), with pleocytosis varying from 10 to 79 cells per c.mm. These findings, in a series of tumours selected because of their strict confinement to the corpus callosum, seem to be of very great importance.

The examination of cerebrospinal fluid in the majority of cerebral tumours gives negative results. Alterations in the cerebrospinal fluid in cerebral tumour appear to take place only when the tumour itself is actually in relation to the cerebrospinal fluid, either in the ventricles or basal cisterns. It can be easily understood that from their situation and vascularity, tumours of the corpus callosum are likely to give rise to direct passage of blood protein and tumour cells into the cerebrospinal fluid. Meningeal or cortical tumours are usually firm, avascular endotheliomata, and they rarely cause any alteration in the fluid in spite of their size. In the multitudinous case reports extant on tumours of the corpus callosum, the records of cerebrospinal fluid examination are incomplete or altogether wanting and, so far as we can ascertain, no other writers have emphasized these changes in the cerebrospinal fluid.

VI.—*Other Symptoms.*

In seven of our fourteen cases the pupils were unequal. In one case the inequality was noticed only during epileptiform fits. In six of our cases some degree of aphasia was present, and in these cases the predominating weakness was always on the right side. In Case 13, in which the predominating weakness was right-sided, aphasia was absent, but here the patient was left-handed. In all cases in which the predominating weakness was left-sided there was no aphasia whatever. In the aphasic cases perseveration was marked, and in Case 9 the patient had echolalia.

VII.—*General Symptomatology.*

Most authors are in agreement with Bristowe that in tumours of the corpus callosum the general signs of increased intracranial pressure of the posterior clinoid processes of the pituitary fossa. Occasionally calcified masses in the neoplasm of the corpus callosum may be visible in the X-ray.

Although we have had but little opportunity for making observations, it would appear that ventriculography has a considerable field in the diagnosis of these median tumours. In Case 7 it established the site of the tumour. Ventricular distortion is an almost constant post-mortem finding and the neoplasm frequently involves the septum lucidum.

LOCALIZATION WITHIN THE CORPUS CALLOSUM.

The diagnosis of tumour of the corpus callosum has been in the past so largely a matter of conjecture, that any attempt to formulate localization of the growth to particular regions of the corpus callosum would appear to be almost too idealistic. We believe that this can be done only in rare instances, in which the clinical picture is distinctive and the "neighbourhood" symptoms well marked. In 1899, however, Schüpfer attempted to draw up criteria distinguishing the portion of the corpus callosum which was invaded by the growth. He stated that tumours of the genu were characterized by: (1) The early development of psychical in relation to motor disturbances; (2) isolated, or early unilateral or bilateral central facial palsy; (3) a tendency of the head to rotate towards the paralysed side; (4) rigidity of the neck muscles; (5) greater paresis in the arms than in the legs; (6) ataxia. Tumours of the middle portion were said to develop a paresis of both upper and lower limbs, progressing to a total paralysis. Tumours of the splenium were marked by: (1) onset of paresis in the lower limbs before the upper limbs; (2) absence of facial paralysis; and (3) a weak, uncertain and ataxic gait.

We have been unable to confirm these observations.

DIFFERENTIAL DIAGNOSIS.

In making the diagnosis of a tumour of the corpus callosum we have to consider, *firstly*, the differentiation from pathological cerebral conditions other than tumour, and *secondly*, the differential diagnosis from tumours in other regions of the brain. The condition most closely simulating the syndrome presented by tumours of the corpus callosum is cerebral arteriosclerosis. The psychical changes, bilateral pyramidal signs, tremor and other involuntary movements may be closely simulated, and, as we have already emphasized, in many cases of corpus callosum tumours the general symptoms of increased intracranial pressure may the genu to the splenium, was discovered as a chance finding. Virchow had called attention to the fact that at the genu and in the neighbourhood of the anterior pillars of the fornix fat may be found normally. Rokitansky described a lipoma the size of a pea in the ependyma of the corpus callosum. Similar cases have been described by Pagliese (1895), Steigert (1902), Würth (1903), and others.

Gliomatous tumours of the corpus callosum do not tend to grow along the striæ. Those of the genu extend into the frontal poles, those of the middle portion into the corpus striatum and downwards towards the third ventricle. It may frequently be noticed that growth into the lateral ventricle is limited by the ependyma of that structure. This was a marked feature in Cases 2, 5 and 10 of our series. Tumours of the splenium tend to extend into the optic thalamus and along the optic radiations, pushing into the body and posterior horns of the lateral ventricles.

Some distortion of the internal capsule in whole or part is almost constantly found, and the lateral ventricles are rarely symmetrical. Unilateral hydrocephalus may be met with from blockage of the foramen of Monro, and in tumours of the splenium obstructive internal hydrocephalus occurs from blockage of the aqueduct of Sylvius. Some degree of internal hydrocephalus may arise, apart from ventricular obstruction, presumably due to deflection of the falx, with consequent compression of the great vein of Galen, thus inducing an excessive production of cerebrospinal fluid.

Thromboses in the distribution of the anterior cerebral artery are met with very frequently. It will be recalled that the main branch of this artery, after giving off the calloso-marginal artery, courses backwards along the indusium of the corpus callosum, supplying the anterior 7/8 of the corpus callosum and the centrum ovale in the region of the head of the caudate nucleus. The two halves of the choroid plexus may be widely separated by growths of the splenium, and this structure may be compressed so that it lies in apposition to the lateral walls of the body of the ventricles.

In Levy-Valensi's series of 74 cases, the growth was located 28 times in the genu, 19 times in the splenium, and 8 times in the body of the corpus callosum. In 19 of these cases the whole of the corpus callosum was involved. In a large series collected by Bruns, growths of the corpus callosum were found three times more frequently in men than in women, and most frequently between the ages of 30 and 40 years.

[11] Chopart, F. "Mémoire sur les lésions de la tête, par contre-coup," Paris, 1771.

[12] Corner, G. W. "Anatomists in Search of the Soul," *Ann. Med. Hist.*, 1919, **2**, 1.

[13] Dejerine, J. J. "Anatomie des centres nerveux," Paris, 1901, **2**.

[14] Dotto and Pusateri. "Sul decorso delle fibre del corpo calloso e dello psalterium," Pisani, Palermo, 1897, **18**.

[15] Eichler, G. "Ein Fall von Balkenmangel im menschlichen Gehirn," *Arch. f. Psychiatr.*, 1878, **8**, 355.

[16] Ferrier, D. "Experiments on the Brain of Monkeys—No. 1," *Proc. Roy. Soc. Lond.*, 1874-1875, **23**, 409.

[17] Flourens, J. P. M. "Recherches expérimentales sur les propriétés et les fonctions du système nerveux," édit. 2, Paris, 1842, p. 21.

[18] Foix and Hillemand. "Les syndrômes de l'artère cérébrale antérieure," *L'Encéphale*, 1925, **20**, 209.

[19] Foville, A. "Traité complet de l'anatomie de la physiologie, et de la pathologie du système nerveux," Paris, 1844.

[20] Gand. Quoted by Mingazzini, "Der Balken," p. 169.

[21] Garrison, F. H. "History of Medicine," 3rd edition, 1921.

[22] Gowers. "Diseases of the Nervous System," 2nd edition, 1893, **2**, 314.

[23] Greenfield and Carmichael. "The Cerebrospinal Fluid in Clinical Diagnosis," London, 1925, p. 187.

[24] Guillain, G. "Sur un cas de tumeur du splénium," *Rev. Neurol.*, 1922, **29**, 23-27.

[25] *Idem. Annales de Méd.*, 1922, **11**, 33.

[26] Haeser, H. "Lehrbuch der Geschichte der Medicin," 3rd edition, Jena, 1875.

[27] Hamilton, D. J. "On the Corpus Callosum in the Adult Human Brain," *Journ. Anat. and Physiol.*, 1884-1885, **19**, 385.

[28] *Idem.* "On the Corpus Callosum in the Embryo," *Brain*, 1885-1886, **8**, 145.

[29] Hartmann, F., jun., and Trendelenburg. "Zur Frage der Bewegungsstörungen nach Balkendurchtrennung an der Katze und am Affen," *Zeitschr. f. d. ges. Exper. Med.*, 1927, **54**.

[30] Henry, M. "Dissection of a Brain, in which the Corpus Callosum, Fornix and Septum Lucidum were Imperfectly Developed," *Medico-Chirurg. Trans. Lond.*, 1848, **31**, 239.

[31] Henschen, S. E. "Pathologie des Gehirns," 2, 415.

[32] Huddleson. "Ein Fall von Balkenmangel mit Lipomentwicklung im Defekt," *Zeitschr. f. d. ges. Neur. u. Psychiatr.*, 1928, **113**, 177.

[33] Kaufmann, E. "Ueber Mangel des Balkens im menschlichen Gehirn," *Arch. f. Psychiatr.*, 1887, **18**, 769, and 1888, **19**, 229.

[34] Koranyi, A. "Ueber die Folgen der Durchschneidung des Hirnbalkens," *Pflüger's Arch. f. Physiol.*, 1890, **47**, 35.

[35] Lafora, G. R., and Prados y Such. "Experimentalversuche über die Function des Gehirnbalkens," *Zeitschr. f. d. ges. Neurol. u. Psychiatr.*, 1923, **84**, 617-641.

[36] Lancisi, J. M. "Dissertatio Altera. De sede Cogitantis Animae," T. 2, Geneva, 1718, p. 302.

[37] La Peyronie, F. G. "Observations par lesquelles on tâche de découvrir la partie du cerveau où l'âme exerce ses fonctions," *Acad. Royale des Sciences, Paris. Mémoires de Mathématique et de Physique.* 1741, p. 199.

[38] *Idem. Mém. et Journal de Travaux*, 1709, p. 609.

[39] Leichtenstern. "Ein Fall von Balkentumor," *Deutsch. med. Wochenschr.*, 1887, **13**, 1128.

[40] Leuret, F., and Gratiolet, L. P. "Anatomie comparée du système nerveux," 1839-57, **2**, 57.

[41] Levy-Valensi, J. "Le corps calleux (étude anatomique, physiologique et clinique)," *Thèse de Paris*, 1910.

[42] *Idem.* "Physiologie du corps calleux," *Presse Méd.*, 1911, **19**, 72.

[43] Lewandowski. "Die Funktionen des zentralen Nervensystems," Jena: Fischer, 1907.

[44] Liepmann, H. "Die linke Hemisphäre und das Handeln," *Münch. med. Wochenschr.*, 1905, **52**, 2322, 2375.

[45] *Idem.* "Ueber die Funktionen des Balkens beim Handeln und die Beziehungen von Aphasie und Apraxie zur Intelligenz," *Med. Klinik*, 1907, **3**, 725; 765.

[46] Magendie, F. "Leçons sur les fonctions et les maladies du système nerveux," 1841, **1**, 181.

[47] Maliverni. "Absence du corps calleux, du septum lucidum et de la circonvolution du corps calleux dans un cerveau," *Gaz. Méd. de Paris*, 1875, 4th Series, **4**, 88.

[48] Marat, J. P. "A Philosophical Essay on Man," London, 1773.

[49] Mellus, E. L. "Bilateral Relations of the Cerebral Cortex," *Johns Hopkins Hosp. Bull.*, 1904, **12**, 108.

[50] Meynert, T. "Neue Studien über die Associationsbündel des Hirnmantel," *Sitzungsb. Akad. Wissensch. in Wien*, 1892, **101**, 3, 361.

[51] Mingazzini, G. "Ueber die Beziehungen zwischen den Balken und den lentikulären Fasern und der inneren Kapsel," *Deutsch. Zeitschr. f. Nervenheilk.*, 1926, **94**, 168.

[51A] *Idem.* "Der Balken," Berlin, 1922.

[52] Moniz, E. "Les tumeurs du corps calleux," *L'Encéphale*, 1927, **22**, 514.

[53] Morgagni, J. B. "Opera Valsalvae (Epistolas additit. duodeviginti)," Venetiis, 1740, 494.

[54] Mott, F. W. "Report on Bilaterally Associated Movements, and on the Functional Relations of the Corpus Callosum to the Motor Cortex," *Brit. Med. Journ.*, 1890, **1**, 1124.

[55] Mott, F. W., and Schafer, E. A. "On Movements resulting from Faradic Excitation of the Corpus Callosum in Monkeys," *Brain*, 1890, **13**, 174.

[56] Muratow, W. "Secundäre Degeneration nach Durchschneidung des Corpus Callosum," *Neurolog. Centralbl.*, 1893, **12**, 316, 714.

[57] Pavlov. "Conditioned Reflexes," Anrep's Translation, Oxford, 1927, 150-352.

[58] Perrault, C. and P. "Œuvres diverses de physique et de mécanique," Leide, 1721, **2**, 403.

[59] Plater, F. "Observationum," Bâle, 1614, **1**, 13.

[60] Preston, C. "An Account of a Child Born Alive without a Brain and the Observables in it on Dissection," *Philosophical Trans., Lond.*, 1695-97, **19**, 457.

[61] Ransom. "On Tumours of the Corpus Callosum," *Brain*, 1895, **18**, 531.

[62] Raymond. "Tumeur du Corps calleux," *Journ. d. Méd. intern.*, 1906, **10**, 268.

[63] Reil, J. C. "Mangel des mittleren und freyen Theils des Balkens im Menschengehirn," *Arch. f. Physiol.*, 1812, **11**, 341.

[64] Rokitansky. See references Mingazzini—"Der Balken," p. 200.

[65] Saucerotte, N. "Mélanges de Chirurgie," Paris, 1801, p. 290.

[66] *Idem.* "Mémoire sur les contrecoups dans les lésions de la tête," *Mém. pour les Prix de l'Acad. Roy. de Chirurgie*, Paris, 1819, **4**, 334.

[67] Schroder, P. "Das fronto-occipitale Associationsbündel," *Monatschr. f. Psychiatr.*, 1901, **9**, 81.

[68] Schupfer. "Sui tumori del corpo calloso," *Riv. sper. di Fren.*, 1899, **25**, 86; 283.

[69] Sherrington, C. S. "On Nerve-tracts Degenerating secondarily to Lesions of the Cortex Cerebri," *Journ. of Physiol.*, 1889, **10**, 429.

[70] Sprengel, K. "Histoire de la médecine," Paris, 1815-20.

[71] Stern. "Die psychischen Störungen," *Arch. f. Psychiatr.*, 1914, **54**, 663.

[72] Ugolotti, F. "Contribuzione allo studio delle vie piramidali nell' uomo," *Riv. sper. di Fren.*, 1901, **27**, 38.

[73] *Idem.* "Sulle vie piramidali dell' uomo," *ibid.*, 1906, **32**, 776.

[74] van Valkenburg, C. T. "Experimental and Pathologico-anatomical Researches on the Corpus Callosum," *Brain*, 1913-14, **36**, 119.

[75] Villaverde. "Beitrag zur Entwicklungsgeschichte des Balkens," *Schweiz. Arch. f. Neurol. u. Psychiat.*, 1919, **4**, 45.

[76] Vieussens, R. "Nevrographia," 1685, 128.

[77] Steiger, A. de. "Two Cases of Lipoma of the Brain," *Journ. Ment. Science*, 1902, **48**, 64.

[78] Wepfer, J. J. "Observationes anatomical ex cadaveribus eorum, quos sustulit apoplexia," 1675, p. 892.

[79] Willis, T. "Cerebri anatome," Lond., 1664.

[80] Wilson, Kinnier. "Contribution to the Study of Apraxia," *Brain*, 1908, **31**, 164-216.

[81] Wurth. "Ein Beitrag zur Histologie und Symptomatologie der Balkentumoren," *Arch. f. Psychiatr.*, 1903, **36**, 651.

[82] Wysocki and Zbyszewski. "Nouvelles recherches sur l'influence réciproque des hémisphères cérébraux," *Compt. rend. Soc. de Biol. de Paris*, 1925, **93**, 1629-1631.

[83] Zinn, J. G. "Dissertation inauguralis," Gottingen, 1749.

SKIN REACTIONS IN A CASE OF CERVICAL SYMPATHETIC PARALYSIS, WITH A NOTE ON THEIR PRACTICAL APPLICATION TO NEUROLOGY.[1]

BY KENNETH E. HARRIS, M.R.C.P.

Medical Registrar, University College Hospital.

(*From the Cardiac Department, University College Hospital.*)

THE skin is innervated by two sets of nerve-fibres, the sensory and the sympathetic. Each has its definite function, and each, at its commencement, takes a different path to reach the skin; the ganglia and the cells lie in different situations and can be damaged separately. The general effects of destruction of each type of nerve are well known. When a sensory nerve is cut or damaged, sensation is lost over the area of skin supplied by that nerve. Sometimes, however, it is difficult to decide where the nerve is damaged; the sensory loss may be due to injury of the nerve, the ganglion or the spinal cord. When a sympathetic nerve is damaged, vaso-dilatation occurs in the area supplied, the pilo-motor spinal reflex is lost and the secretion of sweat is arrested; but again it is not always easy to locate the lesion, which may be in the peripheral part of the sympathetic system, in the ganglion, or central to this. In the case of the sensory nerves the recognized tests are insufficient to show whether the peripheral fibres are degenerate or not; for the sympathetic nerves, this can be determined only by administration of pilocarpine. Recently, however, two simple tests have been made available through the work of Sir Thomas Lewis, Ronald T. Grant and other collaborators [1] [2] on certain reactions of the human skin; these tests should be of value in neurological diagnosis, since they show clearly whether the peripheral nerve-fibres, sensory and sympathetic, are intact or degenerated.

Sensory nerve test.—It has been shown [2] that, when normal skin is injured in any way, for example, by mechanical, thermal or chemical means, it reacts in a definite manner; a triple response of the blood-vessels occurs. At the site of injury a local red spot appears (local vaso-dilatation) followed by whealing (local œdema); around the wheal is a flare (reflex arteriolar flare). It is this flare that is of interest in nerve lesions. In normal skin the flare appears in about fifteen to thirty seconds after the injury as a pale red flush, which gradually increases in intensity and spreads outwards. At its height it is bright scarlet in colour and extends for about 1 to 3 cm. round the injury and has an ill-defined crenated edge. While the local dilatation and increased permeability of the minute vessels giving rise to the local red spot and the wheal are entirely independent of the nervous system, the arteriolar dilatation giving rise to the flare is dependent on a local axon reflex; if the sensory nerve-fibres are degenerated, the flare fails to appear after injuring the skin. Contrary to Müller's view [5] that the flare depends upon the integrity of the spinal reflex arc, Lewis and his co-workers [2] [3] have shown that the flare is not affected by fresh peripheral nerve section, but is abolished after degeneration (recent or remote) of the sensory nerve-fibres; the flare fails to appear from about the sixth day onwards after nerve section. It follows, therefore, that in the case of a patient presenting anæsthesia of more than a week's duration, if a flare appears on the anæsthetic skin after injury, it may be concluded that the peripheral sensory nerve-fibres are intact and that the anæsthesia is either due to a lesion central to the dorsal root ganglion or is hysterical in origin. If the flare fails to appear on anæsthetic skin, it may be concluded definitely that the peripheral sensory nerve-fibres are degenerated.

---

[1] Work undertaken on behalf of the Medical Research Council.

For carrying out the test, a needle scratch forms a suitable injury. [illegible]he flare is not conspicuous on the skin of a limb; it can [illegible]adily by first congesting the veins of the part to render [illegible]otic; then, after injury, the flare appears bright red on a [illegible]ackground, as a result of the increased blood-flow through the [illegible]ted arterioles.

Sympathetic nerve test.—It is well known that erection of the hairs may be produced on the human skin by means of a reflex through the central nervous system; the application of a piece of ice or various other appropriate stimuli to the skin over the spine causes a generalized erection of the hairs, especially if the body is uncovered in a cool room. Failure of goose-skin to appear on a part indicates interruption of the reflex arc, but does not show whether the peripheral sympathetic fibres are degenerate or not. It is also known that if the skin is sharply struck with a ruler, goose-skin appears over the exact area of stimulation; this is a direct response of the pilomotor muscles and occurs even when the peripheral nerves are degenerate. Lewis and

Marvin [4] have recently shown that if the skin is stimulated by means of a strong faradic current, goose-skin appears for a greater or lesser distance around the electrodes. This goose-skin is not the result of a central reflex but is due to the spread of nerve impulses along a plexus of sympathetic fibres in the skin; the absence of this local reaction of the pilomotor mechanism to faradism shows that the sympathetic nerves have degenerated.

To observe this reaction, Lewis and Marvin employ a du Bois Reymond coil connected to a two-volt accumulator, the current from the secondary coil being carried to twin platinum contacts lying 1½ mm. apart. The secondary coil is placed at such a distance that, when the current is led into the unmoistened skin, it is quite painful; a faradic current of this intensity is usually necessary to get full elevation of the hairs. In about four or five seconds the skin begins to show small discrete elevations, best seen when these are obliquely illuminated; these quickly grow in prominence until full goose-skin is manifested in ten to twenty seconds. Upon the fore-arm the area at first involved extends a centimetre or two from the electrodes in every direction, but if the current is maintained it spreads farther in the skin, until it may involve an area approximately circular and six or more centimetres in diameter; on the leg the area is often larger. It is to be noted that faradic stimulation of the skin also produces the typical reaction to injury, the local red spot, the wheal and the surrounding flare appearing in the skin.

Application of the tests.—The practical applicatio [illegible] tests, is illustrated in the following case of sarcoma [illegible] complicated by a cervical sympathetic paralysis an [illegible] paraplegia.

The patient, a girl, aged 18, was admitted to University College Hospit under the care of Mr. W. Trotter in July, 1927. She was pale and thin an had a lump in the left posterior triangle of her neck. This was about eight centimetres in diameter, hard and fixed to the first rib; it was not connected to the spine. The mass extended down into the chest, giving rise to definite physical signs, namely, flattening, impaired percussion note and diminished breath sounds at the left apex; the rest of the chest showed no abnormal physical signs. X-ray examination revealed that the left first rib was much eroded by a neoplasm extending down into the thorax, but the vertebral column was not involved. The Wassermann reaction was negative. An excised portion of the mass was found microscopically to be a round-celled sarcoma. The growth also affected the nervous system at the root of the neck on the left side, the sympathetic nerves being chiefly involved. There was in addition some wasting and weakness of the left upper extremity, especially of the small muscles of the hand; the distribution was compatible with a lesion involving the sixth, seventh and eighth cervical and the first thoracic anterior roots, or the lower two trunks of the brachial plexus. A lesion of the brachial plexus was indicated by the presence of anæsthesia and analgesia on a narrow strip along the ulnar border of the fore-arm and on the inner half of the palm and the fourth and fifth fingers.

Sympathetic nerves.—Slight enophthalmos was present on the left side and the left palpebral fissure was smaller than the right. The left pupil was greatly contracted; the direct and consensual reactions to light were normal and so was the reaction to accommodation. Although both sides of the face were equal in colour, the left side was a little warmer to the touch than the right. The following representative series of thermo-electric readings were all obtained at a sitting:—

	Right	Left	Difference
Forehead	31·3° C.	31·8° C.	0·5° C.
Cheek	31·5° C.	31·8° C.	0·3° C.
Chin	31·7° C.	31·9° C.	0·2° C.

The left arm was also warmer than the right, the differences in temperature being greater than in the case of the face, although the colour of the two arms was the same. Thermo-electric readings on the skin of the arms were as follows:—

	Right	Left	Difference
Forearm	28·0° C.	29·3° C.	1·3° C.
Back of hand	25·7° C.	28·8° C.	3·1° C.
Ring (IV) finger	24·5° C.	30·0° C.	5·5° C.

The spinal pilomotor reflex was tested by applying a piece of ice to the cervical spine. Goose-skin appeared over the body generally and on the right arm. Goose-skin failed to appear on the left fore-arm and on a part of the left upper arm. The line of demarcation was mapped out; this varied slightly during the process of mapping out, but never by more than half an inch. It may be described as starting on the inner side of the arm 2 inches below the anterior fold of the axilla and running up and out towards the point of the shoulder (A, fig. 1); thence passing down the outer border of the arm to just above the elbow (B, fig. 1), and from here obliquely up the posterior aspect of the arm to rejoin the starting point. All skin proximal to this line was covered with goose-skin (see fig. 1). No goose-skin was detected on the fore-arm. The presence or absence of goose-skin on the face was not noted.

The patient had noticed that for about ten weeks before admission to the hospital her left arm did not perspire, though her right did; she had found, however, that both axillæ perspired freely. On one occasion in the ward, it was observed that her right hand was sweating profusely, whereas the left was absolutely dry. Pilocarpine nitrate ($\frac{1}{10}$ gr.), given hypodermically, produced profuse sweating over the body generally and the right upper extremity, but the left hand and fore-arm remained quite dry. The area of skin without sweat secretion corresponded very closely to the area described above where goose-skin failed to appear; it was a little less extensive by about half an inch all the way round the arm. The sweat reactions on the face were not noted.

These facts pointed to interference with the sympathetic nerve supply to the left side of the face and left arm. It was not known whether the peripheral fibres for the face were degenerate or not, but the absence of sweating on the fore-arm after the administration of pilocarpine indicated that here the peripheral nerve-fibres were degenerated.

The sympathetic supply to that area was further tested by local faradization on the same day as ice was applied to the spine. Faradic stimulation of the skin of the left arm failed to produce goose-skin over the same area in which it failed to appear when ice was applied to the spine, and in which sweating was absent after the administration of pilocarpine. Proximal to the line of demarcation already described and everywhere on the right arm good goose-skin developed. On both sides of the face distinct but less extensive goose-skin was obtained. The results of this test confirmed the conclusion that the sympathetic fibres to the arm were degenerated and provided the additional information that the peripheral fibres to the face were intact.

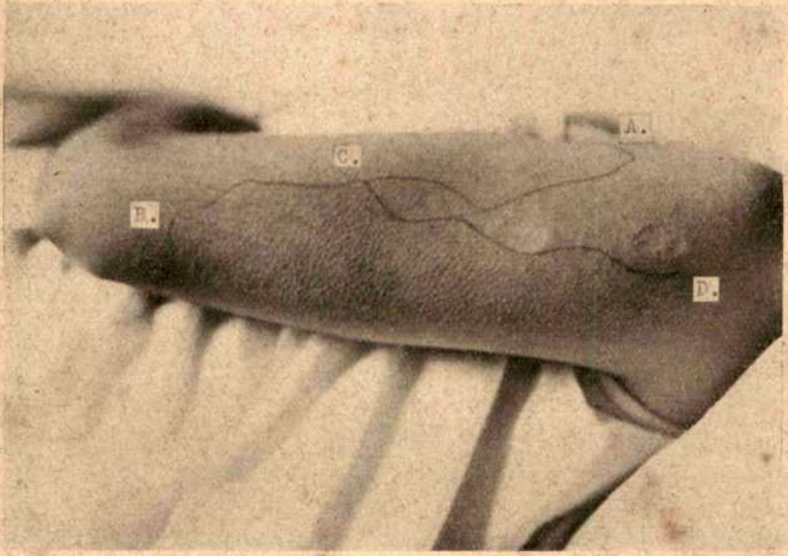


FIG. 1.—Photograph of left upper arm to show the pilomotor response to the application of ice to the cervical spine on November 21, 1927. Distal to the line A—B no goose-skin appeared; goose-skin was more distinct on the posterior aspect of the upper arm behind the line C—D than over the point of the shoulder.

The patient was discharged from the hospital on November 25, 1927, after radium had been applied to the growth in the neck. She was subsequently treated as an out-patient by deep X-ray therapy. Her condition remained unchanged until the end of 1928, when her legs became weak and her gait tottering. She was re-admitted to hospital on November 23, 1928. She was found to have a paraplegia from the second thoracic segment downwards; this was accompanied by retention of urine with overflow. Severe cystitis subsequently developed and the retention gave place to incontinence. She had not wasted greatly since she was first seen in 1927. Evidence of a secondary deposit in her left lung was found clinically, and this was confirmed by X-ray examination of her chest, which showed a large deposit, about 5 cm. in diameter. In the lower cervical region the primary growth was visible as a large mass invading the first and second dorsal vertebræ, as shown by rarefaction of the bodies of these bones. On comparison with the X-rays taken at the end of 1927, it was clear that both these changes were more recent than that date. There was complete loss of movement in both legs; the patient was unable to use her intercostal muscles and employed the diaphragm for respiration. There was no further disturbance of the motor functions of the left arm, as compared with that in 1927. The signs of involvement of the sympathetic nerve supply to left arm and left side of face also remained unchanged; after administra-

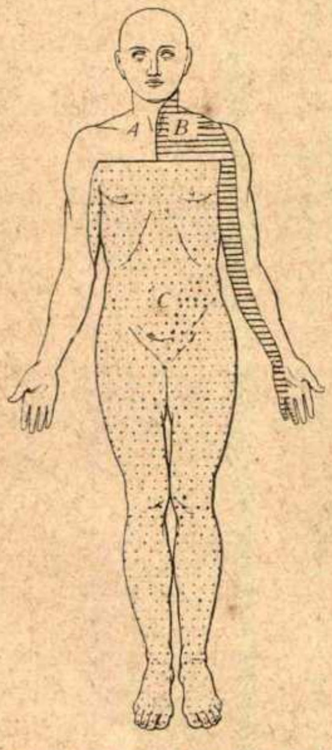


FIG. 2.—Showing area of loss of sensation in December, 1928.

Area A = skin with normal sensation.
Area B = skin anæsthetic as a result of a peripheral nerve lesion.
Area C = skin anæsthetic as a result of a paraplegia.

tion of pilocarpine it was noted that sweating occurred on both sides of the face.

Sensory nerves.—Sensation was lost over the areas shown in fig. 2. The skin of the body (area *C*) was anæsthetic from the second rib downwards on both sides; the anæsthesia extended also to the inner aspect of the right upper arm. On the left upper extremity the loss of sensation (area *B*) extended down the inner half of the whole limb and up on to the shoulder and trunk. The skin of the face, right shoulder and the rest of the right upper limb had normal sensation (area *A*). The sensory loss over area *C* corresponded to that produced by a destructive lesion of the spinal cord at the level of the second dorsal segment, and here the peripheral fibres were presumably intact. Over area *B* the loss on the arm was most probably due to a lesion of the brachial plexus and the peripheral nerves were presumably degenerated.

Further information as to the state of the peripheral nerves was obtained by applying the flare test. Over area *C* a flare developed after scratching the skin; this showed that the peripheral nerves were intact. Over area *B* no flare appeared, confirming the view that the peripheral nerves had here degenerated. Finally, on normal skin (area *A*) the flare and the usual response to injury occurred. These findings are summarized in the table :—

REACTIONS OF THE SKIN TO INJURY.

Site.	*Sensation.*	*Lesion.*	*Flare.*
Area *A* ..	Normal ..	None ..	Present
Area *B* ..	None ..	Nerve ..	Lost
Area *C* ..	None ..	Cord ..	Present

The patient's condition remaining unchanged, she was discharged from hospital on July 2, 1929. She died at home on August 5, 1929, no autopsy being obtained.

SUMMARY.

Two simple skin tests are described, by means of which it can be determined easily whether the peripheral sensory and sympathetic nerve-fibres are degenerate or not. Their application is illustrated in a case of sarcoma of the first rib, complicated by a cervical sympathetic paralysis and later by a paraplegia.

I am indebted to Mr. Wilfred Trotter for leave to investigate this case, and to Sir Thomas Lewis for much valuable advice and help throughout.

REFERENCES.

[1] LEWIS, T. "The Blood-Vessels of the Human Skin and Their Responses," London, 1927.
[2] LEWIS and GRANT. *Heart*, 1924, **11**, 209.
[3] LEWIS, HARRIS and GRANT. *Ibid.*, 1927. **14**, 1.
[4] LEWIS and MARVIN. *Journ. of Physiol.*, 1927, **64**, 87.
[5] MÜLLER, . R. *Deutsch. Zeitschr. f. Nervenheilk.*, 1913, **47-48**, 413.

THE RESPIRATORY RHYTHM IN ITS RELATION TO THE MECHANISM OF THOUGHT.

BY F. L. GOLLA, F.R.C.P.,
AND
S. ANTONOVITCH, M.B., B.S.
(From the Central Pathological Laboratory of the London County Mental Hospitals.)

THE methods hitherto employed in the investigation of the respiratory concomitants of mental activity have been of two types. The total ventilation has been recorded by means of a plethysmograph into which the subject breathes through a mask or mouthpiece, the expired air alone being measured. Another method involves the use of some form of volume recorder strapped round the chest, the respiratory movements being transmitted to a recording tambour.

No one who has experience of the extraordinary sensitiveness of the respiratory mechanism to affective states can doubt that the first method is so liable to subjective variations as to be unsuitable for psychological work. By means of control tests we were able to demonstrate that even with carefully trained subjects any attempt to breathe through an open mouthpiece or mask, that is to say a piece of apparatus which centres the subject's attention on his breathing, invariably gives rise to an abnormal type of respiration, generally associated with hyperpnœa. We feel convinced that for the recording of strictly normal respiration it is essential not only that the apparatus should in no way interfere with perfectly unconscious and unrestricted breathing, but that in addition the subject should, if possible, be unaware of the fact that his respiration is being tested. The use of a plethysmograph of the nature described, with the unavoidable resistance of its inspiratory and expiratory valves as well as that of the tambour itself, is incompatible with such measurements, even apart from the important psychological factor. As corroborative evidence on this point we will only mention the researches of Schall [6] who showed that even a valve with a resistance exceeding 25 mm. of water has a perceptible effect on the respiratory curve.

Turning to the various methods of recording the respiratory movements of the chest and abdomen, it may fairly be urged that none of these can by its very nature give anything approaching a true record. They are all concerned with recording the movements at a restricted level, i.e., that of application, and can give no definite information as to the resultant effect of the dual mechanism on the total ventilation.

With these considerations in view, we adopted the principle of the apparatus first used by Haldane [4] in his experiments on the excitability of the respiratory centre. In Haldane's original method the subject lay in an oblong box with the head outside, the neck passing through a hole in the lid, composed of an upper and a lower segment. An air-tight junction round the neck was obtained by packing with plasticine. By a suitable volume recorder the increase and decrease of air volume in the box, corresponding to expansion and deflation of the chest and abdomen respectively, could be registered. This simple device is quite satisfactory for the investigation of the physiological responses of the respiratory centre, but requires certain modifications to make it suitable for psychological purposes. We therefore constructed a form of apparatus which allows the subject to be comfortably seated and involves a minimum of pressure round the neck. Our first attempt was not quite successful in so far as the recording instrument proved too insensitive to respond to small and rapid respiratory movements, also in that we had considerable difficulty in obtaining a perfectly air-tight joint round the neck. Professor Buckmaster and Mr. Hickman had meanwhile overcome both these difficulties in an apparatus of similar construction which they used for some unpublished work on respiration in the Physiological Laboratory at Bristol. We are indebted to them for the advice that led to the reconstruction of our plethysmograph on lines substantially similar to the apparatus at Bristol. Fig. 1 shows the final form of the apparatus as used in the present experiments. Essentially it consists of a wooden box with a removable lid and front-piece, both of which can be clamped firmly into position by means of large handscrews. All the joints on the box are effected by the interlocking of carefully moulded edges, the corners being in addition padded with strips of felt. The joints have remained wholly air-tight after more than a year's usage. The lid consists of two pieces, the back being fixed to the box, the front being detachable; both have semicircular holes in the centre, which together form the opening for the neck. The lid is inclined at an angle of 73° to the back of the box, this having proved a detail of great importance, since the neck emerges from the lid not vertically but at an angle. A horizontal section of the neck gives an oblong outline, and considerable discomfort to the subject would therefore result should the neck-hole be in the wrong plane while remaining strictly circular. A circle had to be adopted on account of the great difficulty of achieving an air-tight joint with an elliptical aperture. The diameter of the neck-hole is sufficient to allow of about ½ cm. free play with large-sized necks. An air-tight joint round the neck is obtained in the following way: an inflatable rubber collar with an 8-in. circular skirt attached is slipped over the head and inflated so as to fit the neck exactly, without causing pressure and discomfort. The subject having been seated in the box and the front half of the lid clamped on, the skirt is spread evenly over it. A pair of boards consisting of right and left segments, cut so as to cover the lid exactly, are then placed on top and securely bolted down on the lid. The clamping down of the front piece completes the preliminaries. It is a matter of some importance in ensuring the comfort of the subject to test the height of the seat and alter it, if necessary, before fixing the lid in position. Too low a seat, helped by slight sinking into the cushions, is liable to cause the subject to be partially suspended by the chin and so give rise to discomfort and restlessness; while too high a seat brings the shoulders up against the lid and causes undue fatigue of the neck muscles in holding the wholly unsupported head upright. We obviated this latter difficulty by slipping on a second and loosely fitting collar which, when inflated, acts as an air-cushion for the head, allowing of

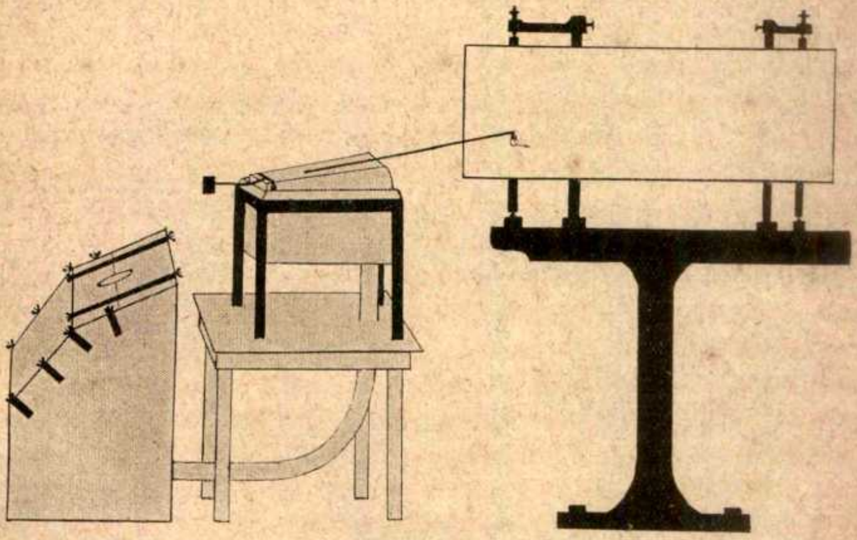


FIG. 1.—Sketch of apparatus.

complete muscular relaxation. A second important point is to pad the box so that the subject has a rest for his back, as otherwise the head tends to bend forward and fall lower and lower. We have had subjects supported in this manner who slept in the box for over two hours without afterwards being aware of stiffness in the neck or any other untoward effects.

The air space in the box communicates with the recording plethysmograph by a wide tube carefully bent so as to avoid acute angles, thus minimizing the resistance to the air current. For this purpose also the tube should be at least 6 cm. in diameter; a smaller bore occasions lag and inadequate sensitiveness of the recorder.

The recorder itself is of the familiar float pattern, rectangular and having a capacity of about 4 litres. The float is balanced on knife edges at its posterior end, the edges resting in corresponding notches on the wall of the trough. A screw projection from the back of the float holds an adjustable weight by means of which the angle of the float and hence the level of the writing point can be altered. A light rod, acting as stylus, is fixed to the top of the float and projects 45 cm. in front. At the end of it is a small writing point fed with red ink which writes on white glazed paper. The up-and-down movement of the lever describes the arc of a circle (with the lever as radius), so that the pointer must be able to swing backwards and forwards on a hinge in order to remain in contact with the vertically placed paper. The front wall of the float is curved, so as to form an arc similar to that represented by the excursion of the lever. The damping effect of the water bath renders the excursions dead beat, while the absence of resistance to the air current allows exceedingly small and rapid movements to be registered.

By means of a small side opening in the box the whole system can be brought into equilibrium with the outside atmosphere before finally making it air-tight and beginning the experiment. The sensitiveness of the apparatus is such that it can be made to show individual heartbeats quite plainly on the respiratory curve.

The excursions of the pointer are calibrated in terms of volume per millimetre excursion, so that an accurate determination of the total ventilation can readily be made when required.

Control tests have shown that slight movements on the part of the subject in the box have no effect on the respiratory record so long as the apparatus remains perfectly air-tight. We always make a point, however, of asking our subjects to keep particularly quiet once they have found a comfortable position, nor did it happen more than once or twice that records had to be discarded on account of movement when reasonable precautions were taken to make the subject as comfortable as possible.

Throughout our experiments we have abstained so far as possible from any suggestion to our subjects that we were investigating the rhythm and volume of respiration. Although the majority of them were either medical students or qualified medical men and women, we found that most of them unhesitatingly accepted the suggestion conveyed in very vague terms that the object of the experiment was a metabolic investigation, and paid no attention to their breathing. We attached great importance to this point at first, since there is no question but that the psychological factor is of great importance in such experiments. However, subsequent observations on ourselves and subjects who had already been experimented on, and therefore knew the purport of the apparatus, have tended to show that under the conditions of the experiment there is little to be feared from the knowledge that respiration is being investigated. By allowing a few minutes to elapse (ten on an average) from the time at which the subject is first seated in the box to the commencement of the actual experiment, it was easy to satisfy ourselves, both by questioning the subjects and examination of the records, that breathing was always normally and unconsciously performed.

SUBJECTS.

The subjects examined were forty-five women and twenty-five men. Of the women thirty were medical students or newly qualified practitioners from the Royal Free Hospital. Of the remainder, five were occupied in scientific work and ten in literary and artistic work. Of the men twenty-two were either medical men attached to the mental hospitals service or trained scientific assistants in the laboratory, one was a young mathematician; one a barrister and one a business man. The great majority of our subjects were therefore trained in a scientific occupation and, with ten exceptions they were under 35 years of age.

In the present series of experiments we found that when the subject sat in an unoccupied state in the box we were at once able to demonstrate the existence of two types of respiration. In the one type the rhythm and the amplitude of the respirations remained absolutely regular; in the other both the rhythm and amplitude were exceedingly irregular. Pauses of varying length occurred between the respirations and the total ventilation might vary several hundred per cent. between any two successive breaths. It was further noted that even in the cases of disturbed respiration the subject tended to maintain the total ventilation over any considerable period at the same level by compensating for a small breath by one or more succeeding large ones, or by following a lengthy pause by respirations of either increased frequency or increased size. This compensation alone, apart from numerous control experiments, demonstrated that the irregularities could not have been caused by movements other than those of respiration, e.g., fidgeting in the box.

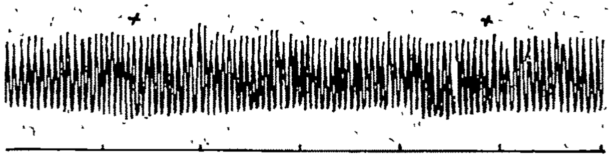


FIG. 2 A.—Respiratory record of a "visual" subject during rest and mental arithmetic. The subject is engaged in adding up columns of figures between the two crosses. Lower line time in minutes. Note the uninterrupted regularity of the breathing at onset and cessation of work. Reduced to ⅓.

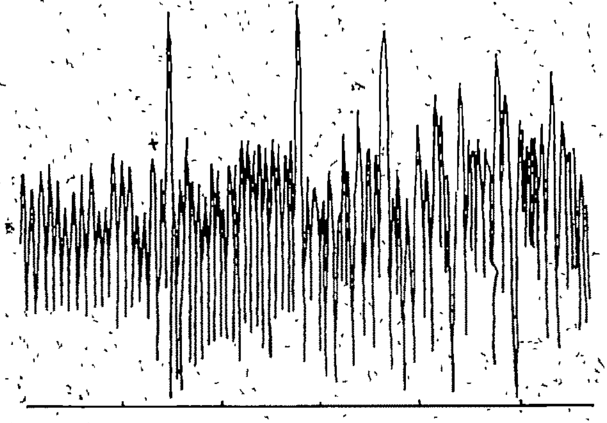


FIG. 2 B.—A record taken under exactly similar circumstances as A and belonging to an "auditory" subject (B). Onset of calculation at the cross mark. Lower line time in minutes. Reduced to ⅓.

It was noted that the type of breathing, regular or irregular, remained constant on repeated examination of any one subject and that it maintained its character even after the subject had been in the box for over an hour. It did not appear likely that such peculiarities in the apparently resting subject could be ascribed to fluctuations of attention.

The next step was to see how subjects of the two types reacted to a task requiring some concentration of attention. For this purpose a page of figures arranged in ten columns (thirty-six in each) for simple addition was placed before the subject. It was found that subjects who had previously exhibited a regular rhythm persisted in this during the performance of the task. In those subjects who showed irregular breathing during the resting stage the performance of the arithmetical task was accompanied by the same or sometimes a higher degree of irregularity in rate and amplitude. The time occupied by the addition averaged seven minutes, and throughout this period the two types of respiratory rhythm maintained their characteristics. The subjects were not enjoined to make any very intense effort; they were asked to aim at accuracy but not to communicate their results. Occasionally during the first few seconds of calculation a more or less complete inhibition of respiration made its appearance. We are not here concerned with this transitory phase, which rarely lasts longer than half a minute and corresponds to the initial increase of tonus with mental effort, and which will be discussed later.

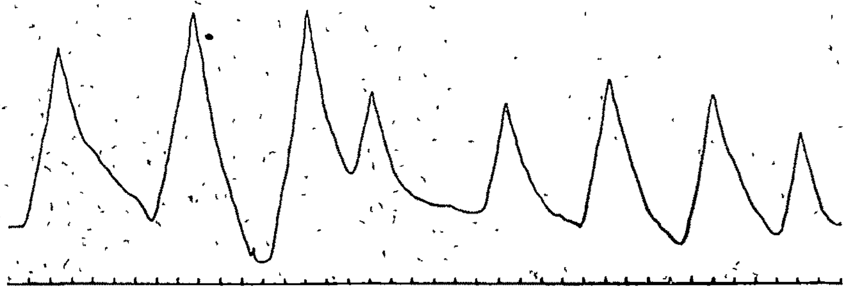


FIG. 3.—Record of subject B at rest, taken at a greater speed. Lower line time in seconds. Reduced to ½.

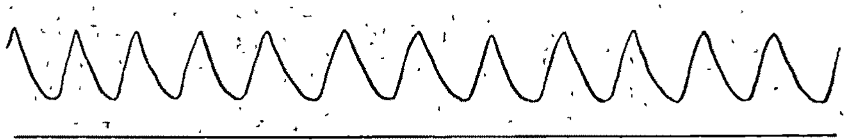


FIG. 4.—Similar record of subject A taken at exactly the same speed. The contrast between the two types is well marked. The differences in size of excursions are due to the fact that subject B is a tall man and subject A a woman of rather less than average height. Reduced to ½.

Fig. 2 shows two very typical records, A being that of a subject exhibiting a markedly regular rhythm, and B of a subject showing great irregularity. It will be observed that addition causes no change in the rhythm of A, whilst in B the irregularity becomes more pronounced. Fig. 3 is a record of irregular respiration of subject B at rest taken at a greater speed. It reveals the complete irregularity of both rhythm and amplitude, with the tendency for succeeding groups of respirations to compensate for variations of their precursors, so as to maintain the total ventilation per unit time at the same level. Careful measurements of the excursions of the lever reveal a complete uniformity of the total ventilation over long periods both in the resting and working subject. Fig. 4, which represents the respirations of subject A during rest, is taken at exactly the same speed as fig. 3, and shows the difference between the two types very strikingly. In the regularly breathing subject the effect of intellectual work is sometimes to cause a uniform lengthening of the expiratory phase, which may be accompanied by an increase in total ventilation without, however, causing an irregularity of the rhythm.

If the two classes of subjects be now asked to recall firstly a piece of poetry and next a piece of music, the reaction is in the main the same as that obtained during calculation; the regular rhythm of the one remains unaltered, and the irregularity of the other is increased. The same result is obtained when the two types are asked to assemble silently the arguments *pro et contra* of an abstract problem, e.g., the freedom of the will.

A concrete problem of the following nature is now set: The subject is asked to imagine that he is given a number of 1-inch cubes which he is to arrange in such a way as to form a large cube measuring 3 in. a side. The large cube is then to be painted red all over and taken to pieces. The problem consists in working out how many of the little cubes will have three sides, two sides, one side painted red, and how many will have no paint at all. The effect of this puzzle on the respiratory rhythm is different from that of an abstract problem. Whilst the subjects with a regular rhythm continue to breathe regularly during the silent unravelling of the problem, the majority, i.e., 80 per cent. of a group of twenty-five irregular breathers, become regular with the onset of this task. Fig. 5 shows the effect of this problem on the respirations of subject B. Of the five who continued to breathe irregularly, two, on being questioned, averred their inability to deal with the problem, which they therefore abandoned, but there is unfortunately no record of the remaining three being questioned on this point.

So far, then, we have distinguished two types of respiratory behaviour, both of which persist whether the subjects be engaged in arithmetical work, in recalling poetry, or music, or in solving an abstract problem, but which alters when a problem involving purely visual imagery is attempted—the regular type persisting, and the irregular type becoming regular.

A total of sixty-seven subjects were examined on these lines, and 45·5 per cent. gave records characterized by an irregular respiratory rhythm, whilst 54·5 per cent. showed a regular rhythm.

The persistence of the two types of respiration under varying circumstances made it appear extremely improbable that the irregularity of the one type was due to fluctuations of attention, while the fact that an irregular rhythm became regular when an attempt was made to solve a problem requiring visual imagery pointed to a relation between the respiratory rhythm and some factors in the mechanism of thought. We therefore proceeded to obtain introspective evidence from each subject as to whether he or she was conscious of relying chiefly on visual or verbal imagery in thought. In this inquiry we were confronted with some difficulties which are less apparent in investigations undertaken on subjects trained in a psychological laboratory. Very few of our subjects had any psychological training or were specially interested in psychological problems; some of them were technicians with only a relatively small amount of the type of education that would be helpful in an introspective inquiry into mental mechanisms. All our subjects were busily employed, many of them in working for examinations, and had at considerable self-sacrifice found the time to attend at the laboratory for the experiments. To have subjected them all to an elaborate questionnaire demanding considerable psychological acumen on the part of the respondent would have been to obtain a small selection of utilizable answers which, for all we knew, might have been representative of only one type of thought mechanism. We therefore decided

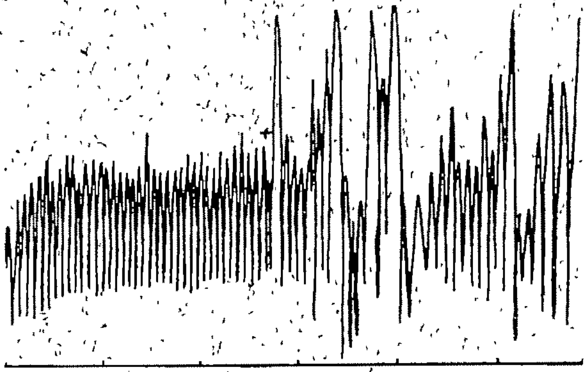


FIG. 5.—Record of subject B while engaged in solving a problem requiring visualization and during subsequent rest. Work to the left of the cross mark, rest to the right. Lower line, time in minutes. Reduced to ⅓.

to submit a few relatively simple questions which would admit of some form of answer from anyone of average intelligence, and to assess the predominant type of thought mechanism on the answers given. These assessments were made without any reference to the plethysmographic records, the correlation of the two being left to the end. The questions which were submitted, either in writing or orally, and on which our assessment was based, were as follows:—

(1) To what extent do you think (*a*) in terms of your own voice, (*b*) in visual images, and (*c*) in terms of movement? Do any of these processes occur simultaneously? If (*a*), are you aware of any throat or tongue movements when thinking?

(2) When you recall a piece of prose or poetry do you hear it or see it? Is it accompanied by visual or auditory images of the events in the piece apart from the actual words?

(3) When you think of a person or object do you first have to recall individual features in order to reconstruct the whole, or do you see them as a whole? If you have to recall individual features do you have to name each before you see it?

(4) In recalling a piece of music do you do so in terms of your own voice or of an instrument?

(5) When calculating how do you represent the figures to yourself?

A number of other questions dealt with points which will be considered later, but it was on the answers to the above five that our subjects were assessed as either predominantly making use of visual or of auditory imagery in thinking. On comparing this classification with the type of record obtained with the plethysmograph, we found that subjects assessed as predominantly visual gave a record of quiet regular breathing, and that those belonging to the auditory type exhibited an irregular respiratory rhythm.

Of the sixty-seven subjects examined introspectively and plethysmographically the records of thirty-four showed a regular respiratory rhythm under all circumstances. Of these, thirty-three were assessed by their own account of themselves as being predominantly visual and one only as belonging to the auditory type. The records of thirty-two subjects showed an irregular respiratory rhythm and of these twenty-eight were assessed by their answers as being of a predominantly auditory type, whilst four were judged to be visual. One record was rejected owing to continuous movement on the part of the subject while in the box, masking the true respiratory picture.

Thus of the sixty-one cases in which records and questionnaire agreed, 54 per cent. belonged to the visual type with regular breathing and 46 per cent. belonged to the auditory type with irregular breathing. Considering the fact that our questions were admittedly lacking in psychological precision, it is surprising that the discrepancies only totalled 7·5 per cent.

The distribution of the two types is about the same in the two sexes. Our sixty-one subjects comprised twenty-one men who were divided into ten of the auditory and eleven visual type, whilst of the forty women twenty-three belonged to the visual and seventeen to the auditory type. Since the overwhelming majority of our subjects were either connected with medicine or science no occupational classification is possible.

THE SIGNIFICANCE OF THE TWO TYPES OF RESPIRATORY RHYTHM.

The fact that irregular breathing becomes regular when a problem such as that of the cubes is set—a problem that can only be solved by visual imagery—is in itself a strong indication that the irregular respiration recorded in the auditory type is causally connected with the predominant use of internal speech, at the existence of which our subjects hint when they say that they think in terms of their own voice. The image here is an auditory one but invariably refers to the subject's own vocal organs. It would, however, be wrong to assume that such irregularity both of rhythm and amplitude of respiration is in any sense a point-to-point representation of the actual respiratory disturbance that would take place were the auditory images to be translated into spoken words. If this were so, such images could only occur, as in speech, during the expiratory phase, whereas anyone belonging to the auditory type is conscious that the images arise uninterruptedly both during expiration and inspiration. Such a person has only to maintain an imaginary argument in terms of internal speech to satisfy himself that the stream of auditory images undergoes no interruption during inspiration. The irregular breathing of an auditory person cannot therefore be regarded as a mere silent reproduction of the respiratory movements that would take place were the words audibly spoken or whispered. That states of emotional and intellectual tension are accompanied by respiratory disturbances has long been known. It is necessary to discuss shortly the possibility of mental tension as a factor influencing respiration.

Our primary object in this investigation had been to see whether any correlation could be found between lapses of attention and disturbances in the respiratory rhythm. The effect of intensive intellectual effort on respiration, such as shallow and quickened breathing, and the occasional occurrence of inhibition in the inspiratory phase, has been repeatedly studied by observers using thoracic and abdominal recorders of the Lehmann type. Zoneff and Meumann [7] from numerous observations on six subjects were able to state that voluntary concentration of attention causes a slowing of the pulse and an inhibition of respiration more marked in the thoracic than in the abdominal type; also that the inhibition appears either in the form of a total cessation, or in a flattening of respiration which is often accompanied by an increased frequency; that the inhibition of respiration and slowing of pulse rate reach a certain maximum intensity, and then, if the experiment be continued, they again become normal or even swing over to the opposite side. They conclude that the alterations of the respiratory rhythm are linked up with fluctuations of attention. One of us [2] in 1921 described similar phenomena and endeavoured to show that they bore a relation to the increased tonus of skeletal muscles which it was possible to demonstrate by myographic methods during intellectual effort and which we have recently confirmed by observations on the tendon reflexes [3]. In all such cases the experiments have been of short duration and the attention has been concentrated with maximum intensity.

Apart from the fact that our experiments were conducted over lengthy periods under conditions which involved no great increase of emotional or intellectual tension, two facts emerge that negative the explanation that respiratory irregularity is due to either or both of these factors. Firstly, the correlation between the auditory type and irregular breathing, and the visual and regular breathing, which would on this hypothesis imply the manifestly absurd assumption that only the auditory type display intellectual and emotional tension. Secondly, that when the auditory type concentrates on a problem that can only be tackled by the use of visual images the respiration becomes regular, except in those subjects who declared that they were unable to conjure up the necessary image and abandoned the attempt to solve the problem.

Can the respiratory irregularity be explained as being due to interference of laryngeal movements accompanying auditory images? One of us has been able to produce objective evidence that such laryngeal movements may occur during the representation of singing up and down an octave, but there is no such objective evidence of their general occurrence during thought processes of the auditory type. Stricker, by introspection and concentration of attention upon his own mental processes, came to the conclusion that the primary revival of word images was by a sense of movement in the muscles of articulation, but, as Mott [5] points out, any such concentration must make the observation of doubtful value. Of our own subjects, ten only were conscious of laryngeal movements during thought, and one described tongue movements. All these subjects, it is to be noted, belong to the auditory or irregularly breathing type, but they form a very small proportion of the total number. It would be unwise, however, to conclude from the fact that the majority of auditives are unconscious of such movements, that they do not occur. As anyone may prove for himself, it is a matter of great difficulty, even when speaking aloud, to apprehend laryngeal movements.

In the absence of any experimental evidence the nature of the connection between irregular breathing and an "auditory" way of thinking must be left an open question. It is at least a possible hypothesis that the continual occurrence of laryngeal movements as an accompaniment or possibly a precursor of verbal images disturbs the respiratory rhythm so as to produce either acceleration or retardation and increased or decreased amplitude of breaths, according to the phase of respiration in which such movements occur.

THE RELATION OF THE TWO RESPIRATORY TYPES TO CERTAIN MENTAL PROCESSES.

By far the simplest mental process with which we are concerned is an ordinary arithmetical operation; addition or subtraction, multiplication or division involve a minimum of valuation. To a great extent simple arithmetical operations are memory processes in which the terms of reference are a highly restricted series of images whose nature will be determined by the type originally employed in the process of learning, be the image a visual, auditory or motor one. An inquiry was made among our two classes of subjects as to their proficiency in mental arithmetic. We were, of course, precluded by the status of our subjects from obtaining information by any direct examination such as might be made with junior students. The subject was simply asked: Are you good at mental arithmetic? Of the fifty who answered this question twenty-two reported themselves as bad and twenty-eight as fair or good. Of the twenty-two "bad" cases fourteen belonged to the auditory (irregular) and eight to the visual (regular) type. Of the twenty-eight "good or fair" ten belonged to the irregular, and eighteen to the regular respiratory type.

It may, therefore, be fairly stated that irregular respiration indicates a type of mind that is on the whole unsuccessful in mental arithmetic; and that the opposite is true of the regular breathers. The connection that we have demonstrated between the type of respiration and the type of image predominant in thinking might at first suggest that the failure of irregular breathers to make good at mental arithmetic was due to their being unable to form visual images of the necessary figures. Such an explanation would, however, be an over-simplification of the problem. When asked how they represented numerals, of fifty subjects who replied to this question eleven reported auditory images alone, and of these six belonged to the irregular and five to the regular breathers. Eight reported mixed auditory and visual images and of these six were of the irregular and two of the regular type. The remaining thirty-one subjects all reported purely visual images and of these nineteen belonged to the regular and twelve to the irregular respiratory type.

The data may be summarized in the following table.

Representation of numbers in terms of	Regular breathers		Irregular breathers		Total
	Mental arithmetic		Mental arithmetic		
	Good	Bad	Good	Bad	
Auditory images	2	3	1	5	11
Visual and auditory images	2	—	4	2	8
Visual only	14	5	5	7	31
Total	18 69·2 %	8 30·8 %	10 41·6 %	14 58·4 %	50

It will be seen that though out of our original sixty-one subjects twenty-eight with irregular respiration had reported themselves as predominantly using auditory images in ordinary thought and thirty-three of the regular type as predominantly visual, the imagery of numbers does not closely follow that of thought generally. It will at the same time be noted, however, that when—owing possibly to methods of education—twelve of the irregular auditory type adopt visual number images they are still less successful in mental arithmetic than the regular type using their predominant visual imagery. A possible explanation is that the first-mentioned type of person visualizes numbers very imperfectly and carries on his mental arithmetic by interpolating verbal processes with the visualized numbers. The fact that his respiration continues to be irregular is in favour of this hypothesis. On the other hand, those few cases of the regular type who have adopted auditory number images do not seem to be as successful in mental arithmetic as the remaining majority of them who retain their visual imagery during calculation. The researches of Galton [1] show how very much further the examination of the visual representation of numbers should be pushed in order to account for divergencies in arithmetical ability between different persons who equally lay claim to visual imagery. The use of what Galton terms "number forms," i.e., the arranging of numbers in various patterns in one's field of vision, which memory faithfully reproduces every time an arithmetical operation is undertaken, is probably nearly as important as the question of what type of number imagery is relied upon. It seems at least a plausible supposition that the mathematical faculty is intimately connected with visualizing powers. A person who need merely refer to a systematically-arranged pattern of figures when called upon to work out an arithmetical problem is manifestly better off than one who has to rely on the slower and more elaborate method of summoning the figures by name, as it were, before they can conveniently be used for reference. Even then it is probably but a transitory image that is evoked, whereas any process beyond the simplest addition or subtraction would require the simultaneous representation of a number of figures persisting over varying intervals of time.

We were not satisfied that under the conditions of our experiments it was possible to obtain statistics of value as to ability in higher mathematics or literature. Answers to our questionnaire on these points might give the impression that ability in both was evenly divided between our two types of subjects, but certain cases in which we had other means of judging tended to show that autobiographical information of this sort is very unreliable. The same remarks apply to proficiency in drawing unsupported by objective corroboration. It was decided for this reason not to push our investigation into specific abilities with reference to the two respiratory types any further.

It seemed, on the other hand, that since we knew a large number of our subjects particularly well, either as pupils, colleagues, or fellow-students, it might be of value to correlate an assessment of their general ability with their respiratory type. Here, again, we could not, with our class of subjects, contemplate any form of investigation on the lines of Spearman. We decided to consider our subjects simply in the unscientific light of general impressions. Those whom we considered as possessing intellectual ability that distinguished them from the mediocre we classed as being of superior intelligence, the remainder as being of average intelligence. It must be our apology for introducing such unscientific methods into a psychological investigation that the experience of daily life shows that such impressionistic assessments do in practice prove of value when a fair degree of intelligence and common sense can be claimed for the assessor. Fifty-four subjects, thirty of the regular (visual) and twenty-four of the irregular (auditory) type, were assessed on the lines indicated, the assessor in forming his judgment being of course ignorant of the type to which any given subject belonged.

It was found that of the thirty of the regular respiratory type, nineteen, or 63 per cent., had more than average intellectual ability; of the twenty-four irregulars eighteen, or 80 per cent., were of more than average intelligence. The type of subjects on whom our investigations were made should obviously furnish a fairly high percentage of persons of superior intelligence. The subject is to be pursued in further investigations conducted by Spearman's methods on a number of scholars.

THE MUSICAL FACULTY.

The presence or absence of the power of correctly appreciating musical tone (the musical ear) admits of a fairly clear-cut answer that should provide definite statistics with even such a superficial form of inquiry as our questionnaire. We had small hopes of finding any difference in the distribution of the musical ear between the two types of breathers, as we were disposed to believe that the presence or absence of this faculty depended upon the anatomical features of the cochlea. The appended results have, however, led us to change our views.

Fifty-two subjects were examined, of whom twenty-four belonged to the irregular type (auditory) and twenty-eight to the visual. Of the former, 46 per cent. reported "no ear"; of the latter, 18 per cent. reported "no ear." The subjects were next asked how they would recall a piece of music—whether in terms of their own voice or in terms of the instruments on which they had heard it played. The results can be tabulated as follows:—

Music recalled in terms of	Regular breathers		Irregular breathers		Total
	Musical ear		Musical ear		
	Good	Bad	Good	Bad	
Own voice	8	4	4	9	20
Instruments	20	1	9	2	32
Total	28 82·1 °/o	5 17·9 °/o	13 54·1 °/o	11 45 9 °/o	52

It would appear, then, that the irregular respiratory type with the predominantly auditive imagery tend in a little more than half the cases to use the same kind of auditory imagery (i.e., thinking in terms of their own voice) for the representation of music, and that this mode of reproduction may in the majority of cases be responsible for a bad musical ear. If this be so, it should be an indication for encouraging children with a "bad ear" to try to represent notes in terms of an instrument rather than by vocal imitation.

POWER OF VISUALIZING FACES.

It might be expected that if our correlation between the types of breathing and types of mental imagery were correct a certain difficulty would be experienced by the auditory type in visualizing the features of absent friends. In answer to our questions, ten subjects of the irregular type reported that when thinking of a person they have first to recall individual features in order to reconstruct the whole, and fourteen that they see the face as a whole. Of twenty-seven visual ("regular") subjects, all claimed to see the face as a whole. Of the ten first-mentioned, every one finds it necessary to evoke the dominant features from which the face is reconstructed by a verbal image. Ten of the fourteen who see the face as a whole are also aware of using some form of auditory image in the process. None of the "regular" subjects confesses to the use of any verbal images in reconstructing a face.

DREAM IMAGERY.

Forty-six subjects were able to give some account of the nature of their dream imagery. Twenty-seven have purely visual dreams, and of these twenty-two belong to the regular type of breathers, the remaining five being of the irregular type. Seventeen have mixed auditory and visual images in their dreams, and of these, six are of the regular and eleven of the irregular type.

Two subjects have purely auditory images and both belong to the irregular type.

THE SENSE OF SMELL.

Though not strictly in the line of this investigation, we mention the effect on respiration of mental representations of various smells. The majority of subjects who confessed to a keen sense of smell showed very slow and prolonged inspirations interrupted by short and rapid expirations when thinking of a pleasant smell, such as that of a rose. If, after a rest, they are asked to imagine some unpleasant smell, e.g., that of the post-mortem room, the rule is an immediate and long expiration, even if the respiratory cycle is thereby interrupted at the beginning of inspiration. The expirations continue to be drawn out as long as the representation of the smell lasts, but after a few seconds the subject usually becomes aware of his disturbed breathing and often guesses the purport of the experiment. On account of this we invariably introduced the question of smells at the end of the experiments. In every case where a pleasant smell failed to produce a response the subject afterwards declared that he was quite unable to imagine it.

THE PERSISTENCE OF THE TWO TYPES OF IMAGERY.

Although no data are obviously possible as to the persistence of our two respiratory types throughout life, our subjects were unanimous in declaring that so far as they knew no change had occurred in their particular type of imagery since childhood. Galton considered that he had evidence of auditory imagery gradually replacing visual imagery with advancing age. As most of our subjects were under 30 years of age and none over 50, it is impossible to control this statement.

GENERAL OBSERVATIONS.

Our inquiry has only been directed to discover a correlation of some type of thought process with the two very distinct respiratory types that have just been described. Up to the present stage we have abstained from a more detailed investigation into the very complex forms of imagery which the researches of Galton and others have demonstrated, and which may throw some further light on our two respiratory types. Of a motor or dynamic imagery, we have found no very definite trace in the superficial inquiry directed to our subjects. We would wish, moreover, to emphasize that we claim to have demonstrated in the case of the irregular type of breathers only the bodily concomitants of certain forms of imagery, forms that constitute not thought in its entirety, but a series of sign-posts which mark the direction of the continuous stream of thought, that is, of the sense of relation of which we have no definite image. Though two streams, marked either by visual or auditory sign-posts, may ultimately arrive at much the same final conclusion in concrete problems, evidence is not wanting to show that psychological and metaphysical speculations will be profoundly influenced by the type of imagery adopted. We would venture, for example, to suggest that the extreme form of behaviourism put forward by its chief exponent is in no small degree influenced by the fact, so apparent in all his writings, that he is an extreme example of thinking in terms of auditory imagery. The possibility of determining by objective methods the predominant type of thought imagery may prove to be of some practical value in assessing the fitness of subjects for certain specialized forms of work.

CONCLUSIONS.

Observations were made on the respiratory volume and rhythm by means of a plethysmograph enclosing the whole body. Two types of habitual respiration have emerged and are approximately equally distributed among normal subjects of both sexes. The irregular respiratory type has been found in subjects with predominantly auditory imagery; the regular type in subjects with predominantly visual imagery. The irregular type has been found to become regular when a problem is tackled the solution of which requires purely visual images.

The regular type are superior to the irregular type in mental arithmetic.

The "ear for music" is found to be more developed in the regular type. The irregular type tend to recall instrumental music in terms of their own voices.

The power of visualizing faces is much better in the regular type.

General ability was found to be higher in the irregular type.

Purely visual dreams are more frequent in the regular type; mixed visual and auditory dream imagery in the irregular type.

In conclusion, we have to thank Professor Buckmaster and Mr. Hickman for advice in improving our apparatus, and our many subjects for their kindness in subjecting themselves to lengthy experiments and to the questionnaire. Our special thanks are also due to the Medical Research Council for a grant which has enabled one of us to undertake collaboration in this piece of research.

BIBLIOGRAPHY.

[1] Galton. "Inquiries into Human Faculty," 1883.

[2] Golla, F. Croonian Lectures, *Lancet*, 1921 (II).

[3] Golla, F., and Antonovitch, S. *Journ. Mental Science*, 1929, **75** (No 309), 234.

[4] Haldane, J. S. "The Regulation of the Lung Ventilation," *Journ. Phys.*, 1905, **32**, 242.

[5] Mott, F. "The Brain and Voice in Speech and Song," London, 1910.

[6] Schall, L. *Zeitschr. f. d. ges. exper. Med.*, 1921, **14**, 322.

[7] Zoneff and Meumann. "Effect of Attention and Mental Work on Respiration," Wundt's "Philosophische Studien," **18**, 1.

ELECTROMYOGRAPHIC STUDIES OF VOLUNTARY MOVEMENTS IN PARALYSIS AGITANS.[1]

BY E. A. BLAKE PRITCHARD, M.D., M.R.C.P.

Assistant in the Medical Unit, University College Hospital and Temporary Assistant Physician to the Hospital for Epilepsy and Paralysis, Maida Vale.

AMONGST the cardinal clinical features of paralysis agitans the most characteristic and constant are:—

(i) an increased resistance to passive movement,
(ii) involuntary tremor of characteristic form,
(iii) certain disorders of voluntary movement; notably, slowness,
(iv) certain typical attitudes.

A certain degree of lack of parallelism in these features, both in the matter of their relative intensity, and in that of the factors by which they are influenced, suggests that disturbance of more than a single mechanism or function is in question, and that we cannot assume them to be but different manifestations of disorder of a single mechanism. For example, we may not assume that tremor is but an intermittent exhibition of rigidity.

In the examination of the problems thus indicated it seemed probable that simultaneous records of the tension development, length and electrical condition of the muscles might throw some light upon the mechanisms whose activity produces, or whose impairment permits, the development of the disease mentioned above. The graphic records obtained from normal subjects and from those presenting signs of Parkinsonism show, upon comparison, certain differences which indicate the existence of several factors in the production of the Parkinsonian state.

The components of the clinical picture studied by the graphic method are tremor, voluntary movement and rigidity, the three being stated in the order of their accessibility to examination.

The tremor.—The rhythm of the tremor is sufficiently slow to permit its study by simple inspection, but graphic recording is essential for purposes of comparison with the electrical responses obtained from the tremulous muscles. Such electrical records show that there occur within the muscle rhythmical outbursts of activity which are synchronous with the mechanical activity which expresses itself as tremor.

---

[1] From the Department of Neurology, University College Hospital.

The voluntary movements.—While simple observation shows these to be abnormally slow in initiation and execution, graphic recording reveals further that they are abnormally steplike or discontinuous in performance. Further, the voluntary movements of normal subjects similarly recorded under comparable circumstances also present a steplike discontinuity of performance not in quality different from that seen in paralysis agitans. A comparable feature in voluntary movement was first described by Schafer in normal subjects [3], and a comparative study of the phenomenon in normal subjects and in those suffering from paralysis agitans led Walshe to suggest that in the latter we see the exaggeration of a discontinuity that is present in the voluntary movements of normal subjects [4].

Electrical records show certain prominent features which are clearly related to those found in myographic records.

The rigidity.—Myographic records of passive flexion and extension of the fore-arm have been made. In making these it is clearly of importance that records so made should be in terms of angular rotation about the elbow-joint: i.e., the force should be a constant couple and not a linear pull, while the record should show equal deflections for equal degrees of rotation of the fore-arm upon the upper-arm.

By the recording of passive movements in this way we are enabled not only to measure various arbitrary degrees of shortening of the muscles concerned, but also to examine the distribution of the resistance to such movement resulting from the rigidity of the muscles. Since the external force is a constant couple, any variations from a theoretically constant angular acceleration must be due (apart from inertia) to variations in the resistance of the muscles stretched, and is proportional at any stage of rotation to the resistance in play at that moment. The recording of rotation at the elbow, and not merely of some linear trajectory of a point on the limb, provides a record in terms of that mechanical function for which in practice the muscles are normally activated.

Records obtained from electrical leads inserted into a muscle subjected to stretching as in the above experiments are of too uncertain value to be usefully assessed, because the gross changes in the length of the muscle entail so much shifting of the electrodes in relation to the muscle tissue that a complex electrical disturbance is produced, in which the actual muscle action-currents are with difficulty recognized.

DESCRIPTION OF THE APPARATUS.

The method adopted for the recording of electrical changes within the muscle during activity was that first described by Adrian and Bronk [1]. A hypodermic needle carrying in its lumen an insulated electrode is pushed through the skin into the underlying muscle. Leads are taken from the needle and from the electrode passing through it and connected to the input terminals of an amplifying apparatus. The amplified output from this is connected both to a loud-speaker and to a a Matthews' oscillograph. When the muscle is active, a change of potential occurring in the immediate neighbourhood of the electrode gives after amplification, an induced current in the loud-speaker which produces a "crack" or a "pop," and a deflection of the oscillograph mirror which may be recorded photographically.

The standard practice has been to get the subject of the experiment either to contract his muscle as steadily as possible against a certain constant force, or else to vary the tension in his muscle gradually and progressively between certain limits. The deflections of the oscillograph are photographed while this is being done.

Some of the components of this apparatus were of standard type, some were convenient modifications of previously described units, and others were devised especially for this particular work. Each in turn will be shortly described.

The external insulation.—The patient and the apparatus in direct connection with him is entirely enclosed within a rectangular cage made of perforated zinc supported upon a light wooden framework. This is 8 ft. long, 6 ft. high and 3 ft. wide, and can accommodate either a table and a chair, a couch, or a standard bench for animal experiments. It is connected to earth independently through an unearthed pipe.

A second cage of the same material completely encloses the amplifying apparatus together with all the batteries and leads which are used in connection with this. It, also, is earthed independently in the same way.

The loud-speaker is contained in a wooden box which is lined with zinc, and the lining is earthed by connecting it to the insulating cage around the amplifying unit.

The connections between these three insulating-surrounds, and with the oscillograph, consist of lead-covered cables, the covering being in every case earthed.

The muscle "Tensometer." (Fig. 1).—The subject sits upon a chair close up to a heavy table so placed that he can rest his chest against the edge of this and rest both arms completely supported with the fore-arms and upper-arms lying upon its surface.

Upon the top of this table, which is covered with linoleum, is placed the apparatus against which the subject makes those voluntary tension efforts which lead to contraction of his triceps muscle. It can be bolted through the table top in two positions to allow of its use with either arm. It consists of a flat plate of $\frac{3}{16}$ in. brass on which is bolted a small hand vice so placed that its jaws are vertical. Within those jaws can be clamped any one of a series of laminar springs. This spring then extends above the length of the brass plate but is free from contact with it. When a pressure is made in a horizontal direction against its free end it bends to a degree determined by its rigidity and the force exerted. As it yields, it passes beneath a brass arc supported horizontally upon two pillars, one at each side of the base. This arc carries upon its flat upper surface a scale indicating the various degrees of deformity of the spring. The scale is calibrated in terms of grammes and kilogrammes pressure by clamping the base plate vertically and hanging weights from the free end, the plate being clamped on each occasion at such an angle that the pull is perpendicular to the surface of the free end of the spring.

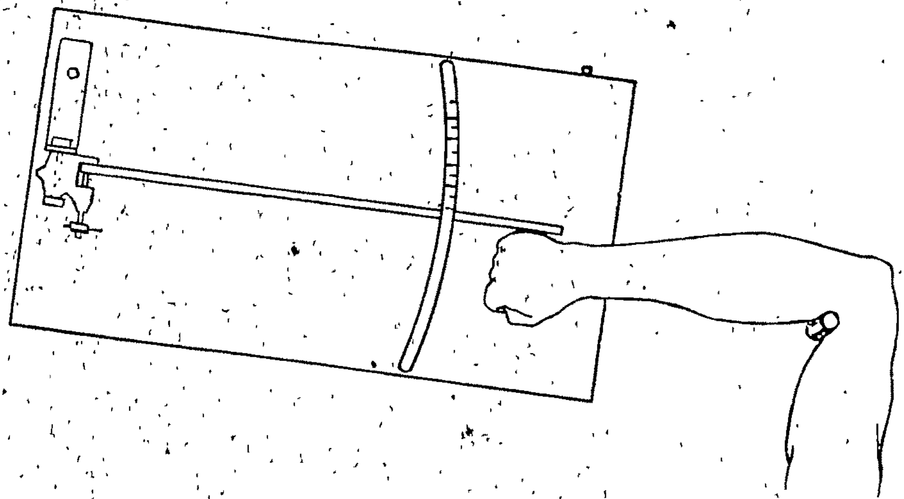


FIG. 1.—A drawing of the apparatus used for controlling muscle tension during active contractions, described in the text.

When in use the base is bolted through the table at one point near the fixed clamp or vice; it is supported in the direction in which the force against the spring tends to make it turn by a movable stop which can be adjusted so that the base and the scale which it carries are in such a position that the spring, at its free end, is approximately perpendicular to the direction of the push which maintains it at each required degree of deformity. This adjustment, taken together with the method of scale-calibration just described, ensures that comparable measurements are being made of the push exerted by the contracting muscle in every case.

By this adjustment of the base-plate and by substituting different laminar springs, for each of which the scale is calibrated anew, the apparatus may be made to resist any desired force exerted by the muscle in a constant direction.

The scale is illuminated by a small electric lamp run from a dry battery and is viewed by the subject through a mirror and a large hand lens, each supported upon the table. When a particular tension is required in the extensors of the fore-arm, he is directed to push against the spring until its upper edge appears to coincide with a corresponding mark on the scale. The position of the base is then adjusted so that this pressure can be maintained with the arm and fore-arm at right angles with each other. A progressive change of tension may be recorded either approximately, by getting the subject to push the spring gradually across the scale, or more exactly by getting him to resist its increasing elastic restoring force as the base is uniformly moved so that the deformation of the spring is increased.

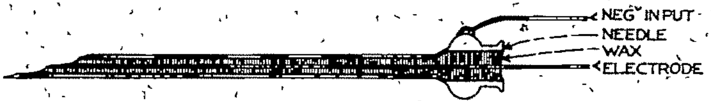


FIG. 2.—A drawing of the concentric muscle electrode, after Adrian and Bronk [1] (modified).

The electrode. (Fig. 2).—This is of the needle type described by Adrian and Bronk [1]. For the records here described it was made in the following way. A length of No. 36 enamelled wire was pushed through the lumen of a hypodermic needle 3·5 cm. long, to the base of which a stout piece of silk-covered wire has been soldered. The needle was then fitted on to the nozzle of a 10-c.c. syringe with the enamelled wire passing up into its barrel. Some paraffin wax was put into the syringe beneath the piston and the whole placed in an incubator until the wax was melted. Pushing down the piston then carried the wax along the enclosed wire through the needle, so that when the whole was allowed to cool the central electrode was insulated by both its enamel covering and by the paraffin wax which otherwise filled the lumen and base of the needle. In those cases in which this had been successful the wire was at one end cut off short at the tip of the needle and at the other wound twice round its base and secured with a strip of adhesive tape. The insulation, and the presence of an exposed surface just short of the needle's point, were tested with a battery and lamp before using.

The needle was pushed into the outer side of the arm at a spot where palpation readily revealed a local swelling and hardening of the triceps muscle with voluntary effort. The skin was treated first with tincture of iodine which was allowed to dry; through it the needle could always be thrust without more than negligible discomfort. The needles were kept in pure lysol, and immediately before use were wiped over with 2 per cent. lysol.

The amplifying apparatus.—This is the standard amplifying unit supplied by the Clifton Instrument Company for use with the Matthews' Oscillograph, and was used in accordance with the directions advised by them. The boxes of valves and batteries necessary for their use will not be described in detail. The lead from the hypodermic needle itself was connected to the negative input of the first box of valves—this side of the circuit being earthed. That from the electrode was connected to the positive terminal of the input.

Only three of the four amplifying valves in cascade were used for obtaining these records, and with these the rheostat control had to be adjusted so that their effect was never maximal. The first box, although padded inside, had to be further protected by being stood upon rubber matting and covered with cotton-wool blanketing—without this the auditory vibrations from the loud speaker were sufficient to set up "howling" and oscillation with any but minimal amplification.

Of the final four valves, three were led off to the coils around the oscillograph, and the fourth was connected with the loud speaker. A special cable and terminal block were supplied for this purpose.

The recording apparatus.—A pointolite lamp was focused upon the mirror of the oscillograph and its light reflected on to the aperture of a moving film camera 5 m. distant, where a circular field of illumination was cast 20 cm. in diameter. The shadow of a vertical bar placed between the lamp and the oscillograph was cast upon the camera. The record obtained consisted of the horizontal movements of the edge of this vertical shadow.

To avoid mechanical vibrations, both the oscillograph and the vertical bar were stood upon heavy iron stands provided with fine vertical adjusting screws and having tripod bases. Each foot of the base was supported upon the bottom of an upturned crucible resting upon a thick layer of "Sorbo" rubber matting. In this way it was found possible to eliminate all noticeable mechanical vibrations except those set up by a heavy blow upon the bench which carried the tripods, and in the absence of any electrical variation the base line was clear-cut and linear.

Time intervals were recorded upon the film by allowing the prong of an electrically-driven tuning fork to intercept the light at one edge.

Apparatus for the graphical recording of arm movements. (Fig. 3).—

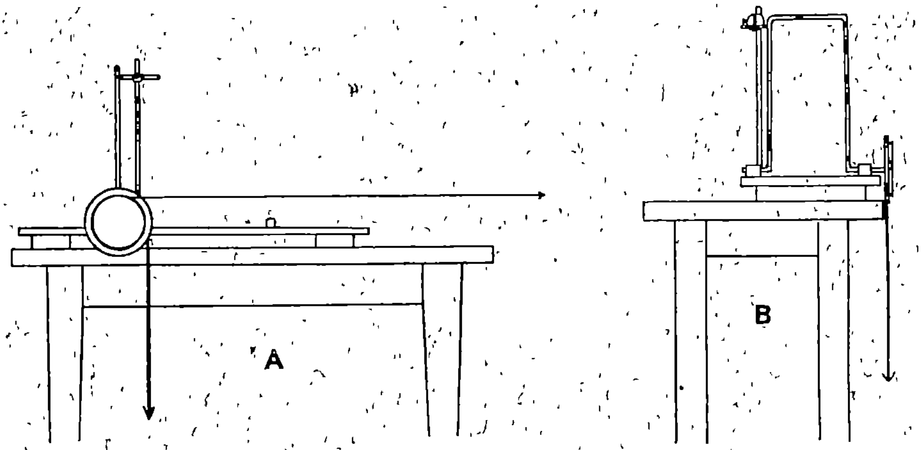


FIG. 3.—A drawing of the apparatus used for graphical recording of active and passive movements of the fore-arm. *A*, lateral view : *B*, end-on view. Described in text.

A piece of iron bar bent into a rectangular framework is supported at each end upon lubricated bearings clamped at either side of a narrow wooden board. One end passes some distance beyond the bearing and serves as the axle for a rigidly attached pulley wheel. This wheel is made up of a number of discs of differing diameters each grooved at its circumference. A steel cable which supports a heavy weight passes over the edge of the largest pulley disc and is tied on to the axle. A fine stout thread is used to connect one of the other pulley discs to the kymograph, that disc being chosen which gives the most convenient size of record. As the framework is rotated about its bearings the weight is raised or lowered and the recording thread is wound on to or off the pulley.

A vertical support screwed into the same board carries at its upper end a horizontally hinged bar which can be made to engage with the rotating framework above. It may be used as a stop to hold this in the vertical position against the force exerted by the hanging weight. A similar stop is fixed further along the board in such a position that it can hold the framework down in the horizontal position against the weight when this is so directed around the pulley that it tends to bring it into the vertical.

When the stop which is temporarily acting as a support is suddenly removed, the framework rotates through a quadrant and is arrested in the case of upward movement by the other stop, in the case of downward movement by a rubber buffer glued on to the wooden base. A soft pad acts as a comfortable rest for the elbow. The table is at such a height that a patient sitting upon a chair at its side can rest his elbow upon the pad with his upper arm at 45° with the horizontal. The pad raises the elbow so that the axis of rotation of this joint coincides with that of the framework. The fore-arm rises vertically from the elbow-joint with the shoulder externally rotated, and in this position the wrist rests against the middle of the framework when this is held by the upper stop. The wrist is fixed to the bar at this point by means of a padded leather strap.

In this way the fore-arm can be made to lie in the plane of the rectangular framework and to follow it passively or to move it actively, the force between the arm and the frame being at all stages of movement directed perpendicular to the arm at a constant distance from the elbow. The angle between the fore-arm and upper-arm varies between 45° and 135°.

The records obtained are those of flexion and extension at the elbow-joint, not of shortening and lengthening of any particular muscle. As it was the form of movement which was chiefly being investigated this was considered not to be a disadvantage. Where rigidity or resistance to passive movements is being recorded no inference can be drawn as to any relation between the resistance offered by the muscles and their degree of lengthening.

The apparatus was used for three different types of record, those showing:—

(i) Rigidity, as resistance to passive movement.

(ii) The continuous or discontinuous character of the voluntary movements.

(iii) The maximum rate of voluntary movements.

The results of measurements of rigidity and of the maximum rate of movement form the subject of another paper in course of preparation. The form of the slow voluntary movements alone is here considered.

The continuity of voluntary movements was recorded by directing the subject gradually and uniformly to flex and then to extend his forearm. The efforts could be made with the framework unloaded or loaded with any desired weight pulling in the direction of either flexion or of extension. The records here shown were all obtained as efforts at uniform contraction and relaxation of the fore-arm flexors against a steady couple tending to produce extension.

For the routine recording of voluntary movements the loading of the apparatus was arranged so that normal subjects were able to carry out gradual flexion and extension of the fore-arm yielding curves which showed no break in the general smoothness. This was necessary because when the load is very much increased so that these movements require all the strength which the subject can exert, even normal persons show an intermittency of contraction recorded as curves showing the same steppage effect as is shown by Parkinsonian patients when much less effort is being made.

The results.—When the electrode-bearing needle is inserted into the triceps of a normal subject whose arm, fully supported upon a horizontal surface, is in complete voluntary relaxation, no disturbances are audible in the loud-speaker and none are recorded upon the oscillograph tracing.

When the needle is similarly inserted into a paralysis agitans patient the same obtains in the absence of visible or palpable tremor.

However, when tremor is sufficiently active, there is received from the loud-speaker a series of sounds each resembling a brisk "rumble," and each repeated at regular intervals in a rhythmical series completely synchronous as far as the ear can detect with the tremulous excursions of the arm from which the lead is taken. At the same time deflections of the oscillograph beam occur which, when photographed, show that each tremor contraction of the muscle corresponds to an outburst of activity such as would be expected if a volley of impulses was arriving at rhythmically spaced intervals, the rhythm being identical with that which may be graphically recorded from the limb segment moved. Such records have the general appearance shown in fig. 4.

When a normal subject, into whose triceps muscle an electrode-bearing needle has been inserted, attempts to extend his elbow against some comparatively immovable support the previously silent loud-speaker and quiescent oscillograph become active, a series of sounds is received from the former and a series of deflections appear in the latter. These have been already described by Adrian and Bronk [1]. If the subject attempts to maintain in his triceps just sufficient minimal active tension for producing a constant stream of sounds from the loud-speaker, the camera records a series of deflections from the oscillograph of equal height and occasionally of regular rhythm or rhythms (fig. 5). As the tension is progressively increased the record (fig. 6*a*) shows, in the early stages of this increase, the addition of other series of regularly spaced deflections, each series appearing at no definite phase interval with relation to the other series already present. A stage is soon reached (fig. 6*b*) at which the deflections increase considerably in average amplitude and at the same time occur so frequently, with such varying degrees of overlap and summation that regular series are no longer with certainty detectable, although a measurement of the total number occurring per second shows that this continues to increase as the tension rises.

When the effort is very greatly increased and the active tension developed in the muscle becomes very large, there appears in all normal persons a tremulous maintenance of this tension. If the muscle is pulling against a strong spring, the slight distortion of which may be used to give a record of isometric muscle contractions, it is found that the tension fluctuates partly regularly and partly irregularly about the level at which an effort is being made to maintain it. A tremulous graphical record such as this may be obtained simultaneously with a deflection record from the oscillograph (fig. 7) which shows that there are outbursts of discharge alternating with periods of comparative quiescence. The frequency of these outbursts is identical with that of the tremulous graphical record. Such an oscillograph record suggests that in these circumstances the deflections are grouped together at intervals and are provided by discharges from within the muscle which, instead of being quite irregular in size and aperiodic, are volleyed from the muscle in groups of comparable amplitude.

When the experiment is repeated with a paralysis agitans patient substituted for the normal subject certain differences in the oscillograph records and loud-speaker sounds are noticed.

Discharges of low frequency and regularity both as regards amplitude and spacing are comparatively rare. Either such response at minimal active muscle tension are uncommon or else such patients show a greater difficulty in achieving and in maintaining such slight degrees of activation of their muscles.

The deflections tend to occur, both at low and at high frequency, in groups. These groups may be either wholly irregularly, or in part regularly, spaced. They occur in nearly all such patients when the tension developed is considerable and may show this phenomenon of grouping or volleying of the discharge at quite low tensions. The patients in whom the volleying is best marked at higher tensions are those in whom it appears also at the lowest degree of tension development and becomes progressively more obvious as this is increased (fig. 8).

Such volleying is always maximal while a constant active tension is being maintained at any particular level. If the muscle tension, after being kept constant along one level, is progressively increased to a higher level at which it is then again kept constant, the volleying of the discharge, well-marked at the constantly maintained, lower level, tends to disappear while the tension is increasing and to reappear at the maintained higher level (fig. 9). During the phase of tension-increase the oscillograph record bears a much closer resemblance to those of normal subjects, i.e., the deflections are all out of step one with the other and of widely differing heights owing to fortuitous overlap and summation.

INTERPRETATION AND DISCUSSION.

When the needle carrying an electrode is inserted into the muscle of either a normal subject or a paralysis agitans patient an electrical discharge can be recorded only if the muscle is

(i) being actually contracted,

(ii) engaged in visible and palpable tremor.

This suggests that the discharge recorded is associated in some way with voluntary or involuntary muscle activity.

If the muscle, while voluntarily relaxed and not showing tremor, is passively stretched and allowed to shorten again, gross changes in the base line of the oscillograph record are obtained (fig. 12), but none of the quick deflections typically associated with muscular activity. Such gross changes may be put down to shifting of the electrode within the substance of the muscle.

It has yet to be decided whether the quick deflections met with during activity of the muscle, either voluntary or involuntary, are due to such mechanical alterations in the relative position of the muscle and of the electrode occurring at a much higher rate, or to that activity of the muscle fibres which provides the development of tension, i.e., the tendency to contract.

The quick deflections occur not only when the muscle is shortening or lengthening but also when it is being kept at a constant tension. If they are due to mechanical shifting of the electrode at a very rapid rate it follows that there must be relative movements of the fibres or groups of fibres within the muscle if not of the whole muscle itself. In the case in which the whole muscle is maintained at a constant length the relative movements of its parts must be summing in such a way that the shortening effect of those fibres which are contracting is at any instant exactly counterbalanced by the lengthening effect of those which are relaxing.

We know that when a muscle is stimulated by a break shock from an induction-coil delivered over its "motor point" it responds by shortening and then relaxing. This sudden twitch of the muscle is provided by the simultaneous stimulation of a number of motor neurones and the simultaneous activity of many muscle fibres. If a series of such stimuli are provided at an increasing, regular frequency, the muscle relaxes less and less completely after each contraction until a stage is reached at which shortening is maintained and no relaxation can be seen to occur. At this point an increase in the strength of the stimuli supplied leads to a raising of the level at which tetanus is occurring but does not lead to any breaking up of the tetanic plateau.

Since an artificial stimulus of this nature throws into activity a number of muscle fibre units, perhaps with different intensities according to their accessibility to the stimulus, but each at the same instant, the total amount of shortening shown by the muscle must be equal to the sum of the shortening of its separate parts.

If a regular series of such stimuli in rapid succession are delivered, the muscle fibres which are in any measure activated will continue to contract and relax together provided their refractory periods do not widely differ. Therefore if such a series produces maintained shortening of the muscle as a whole, it follows that it must be occurring at such a rate that the muscle fibres themselves do not relax in between the stimuli but remain each in a state of maintained contraction. Yet the oscillograph continues (fig. 10) to show a series of deflections synchronous with the stimuli coming from the muscle fibres. Therefore in these circumstances, at least, the electrical changes recorded must be due to the constant contractile activity of the muscle fibres and not merely to shifting of the electrode within the muscle.

When a muscle is maintained by voluntary effort in a state of steady tension there is probably some rotation of activity amongst its fibres, and it is not suggested that the same fibres are always called into play and remain contracted to provide any one degree of shortening. But it is suggested that the fibres which are at any one moment keeping the muscle in a state of steady contraction are themselves all in a condition of maintained shortening (apart from those few which may be actually falling out of, or coming in to, activity in course of rotation). If this be so, then the deflections recorded in this case also must be referred to the contraction process itself and not to mechanical shifting of the muscle fibres beneath that part of the electrode.

Some light is also thrown upon this explanation by the results of leading from animal muscle-nerve preparations. If the tendo Achillis be freed from its insertion into the calcaneus and pulled upon, from a needle electrode placed into either the soleus or the gastrocnemius, deflections are set up in the galvanometer of a slow type, mounting while the pull operates and falling while it is being released.

If the sciatic nerve trunk is dissected out and stimulated with repeated break shocks, the contractions of the soleus and gastrocnemius may be registered graphically through the tendo Achillis. For each contraction a deflection can be received from the oscillograph with the electrode placed in either muscle. Each stimulus gives rise to a single contraction and a single oscillograph deflection (fig. 10). Each deflection might be regarded as being due to the alteration of length of the muscles at each contraction, its much more abrupt form being the result of an active change of shape which is much more rapid than that which can be passively produced by pulling upon the tendon.

The observations show that this is in fact not a reasonable explanation for these deflections.

When the muscle is tetanized into a state of maintained shortening the electrical disturbances continue to follow accurately the rate of stimulation as described above.

When the two heads of the gastrocnemius muscle are left attached to the same tendon and the nerve supply to one of them, e.g., the lateral head, is cut, stimulation of the sciatic trunk is followed by deflection of the oscillograph only when the needle is in contact with that part of the muscle to which the nerve supply is intact, in this case the medial head. Yet the lateral head being still attached to the same tendon moves, without contracting, with each alteration of length of the medial head. No deflections can be recorded from it as a result of stimulation of the sciatic nerve, but the typical slow shifts of the base line still occur when the tendo Achillis is passively pulled upon.

The slow shifts of the base line produced by passive movements whether in animals or in man are in one direction only, i.e., they resemble long drawn out monophasic responses (fig. 11). The deflections described as associated with active contraction of the muscle fibres are displasic in form.

It therefore seems highly probable that the deflections recorded from human subjects in the way above described are the result of electrical changes within the muscle associated with the contractile activities of its fibres.

If we seek to interpret the records obtained from normal persons we have to bear in mind the following observations:—

(1) At low tensions voluntarily maintained the discharge consists of one or more regularly spaced series of disturbances.

(2) At low tensions also the size of these disturbances shows a remarkable constancy both as regards different series and as regards the individual members of any one series.

(3) Where overlapping of such disturbances from different series occurs they summate to give a deflection of increased height.

(4) When the tension is increased the total number of disturbances at first increases, while the series in which they occur remain completely out of step and they remain of approximately unaltered size.

(5) As the tension is still further raised a stage is reached at which the deflections are all of much increased amplitude but are still quite irregularly spaced.

(6) When the tension is finally raised to near its maximum the deflections tend to be thrown together into groups and the discharge from the muscle occurs in volleys. This stage corresponds to the development of tremulous effort in the graphical records of muscle tension.

It is, therefore, suggested that the regular series of infrequent deflections of equal and small amplitude, which can, with facility, be obtained from most normal persons when assisted by the help of the loud-speaker sounds as a control upon their effort output, is produced by a series of regularly spaced and equal discharges from the muscle, originating in the action currents furnished by outbursts of activity in some small unit of the muscle in the immediate neighbourhood of the electrode. Those small units may be either single muscle fibres or else groups of two or three fibres which are normally always activated simultaneously as a unit.

The fact that the size of the deflections varies imperceptibly from series to series at such minimal tensions, suggests that the units activated on such occasions all consist of about the same number of muscle fibres.

It is possible that the rate of discharge from such units during minimal contraction of the muscle is not the greatest of which they are capable and that therefore the interruption of one rhythm and the substitution of another or of a series of aperiodic deflections cannot necessarily be ascribed to the switching over from one unit to another.

Also the deflections caused by discharges of equal size, but taking place from units at different distances from, or differently related to, the electrode will not themselves be equal.

Therefore it is probable that a series of deflections of identical amplitude are set up by action currents occurring in the same muscle unit.

When the tension within the muscle is voluntarily increased each unit begins to fire off more rapidly and other units come into operation. While the occasional occurrence of a deflection of greater amplitude at low tensions may be reasonably regarded as due to the chance overlap of discharge from different units, the records from muscles at higher tensions in which the deflections are all of much greater amplitude cannot reasonably be so explained, and it is suggested that at such increased tensions a progressive fusion of several units into synchronously operated larger groups takes place—the discharge from these being in all cases greater.

As the tension is still further increased this process of synchronization of smaller units into larger groups continues and is at first complete as far as the records here obtained can show, i.e., the larger deflections show no sign, as far as their geometrical form is concerned, of their complexity of origin from different units. There is, however, evidently a limit to this completeness of fusion, i.e , a limit to the number of units which can be simultaneously activated, and the synchronism, complete for small groups, is only partial for larger groups, and the discharges, not falling exactly simultaneously, provide those volleys which are characteristic of the maximal tensions.

It is possible that this limit is not a function of the muscle fibres but one imposed by the neuronic connections either in the peripheral nervous pathway or at a higher level. This, however, is a speculation which further experiments must investigate.

Another observation not previously here mentioned supports this line of explanation. It is that when, during slight voluntary activation of a muscle such as the triceps, involuntary fibrillation of the muscle occurs, each twitch of that part of the muscle belly into which the electrode needle is inserted is accompanied by an extra loud "pop" from the loud-speaker, and an abnormally large deflection upon the record (fig. 13). Here at least we have evidence of the simultaneous discharge of a large group of muscle fibres in the immediate neighbourhood of the electrode which raises a visible knot upon the surface of the muscle and initiates a discharge of increased size comparable to those obtained from the same muscle at much higher degrees of voluntary activation.

In all cases in the course of this work in which electrical records have been obtained from muscles in active contraction, shortening has not been permitted to any extent. The disturbances of movement shown by patients suffering from paralysis agitans on the other hand necessarily appear with the muscle in approximately isotonic activity. In attempting to explain these clinical findings in terms of experimental results this difference demands attention. We know from the work of Adrian that afferent impulses arising in a muscle during its contraction do influence the discharge of motor efferents to that same muscle when the preparation is for these purposes intact, and it is therefore possible that the volleying of such efferent impulses which we have found to be characteristic of sustained isometric contractions in paralysis agitans patients may be influenced by afferents from the muscle which are not similarly active when the muscle contracts isotonically and movement of the limb segments is permitted.

It is extremely improbable, however, that the whole effect is contributed entirely by the isometric conditions of recording the tension development. Thus the tremor records from a limb in voluntary relaxation showed shifts of the base line associated with the tremulous excursions of the limb and also typical action current deflections which are characteristically volleyed. Further, those patients whose electrical records show a well-marked tendency to volleying all yield a tremulous graphical record of active flexion and extension.

Therefore it seems reasonable to suppose that just as constant active maintenance of tension within the muscle depends upon a relative asynchronism of activation of the muscle elements, so also does the ease with which gradual changes in length of the muscle are provided or permitted by contraction or relaxation, and hence the smooth execution of voluntary movements, depend upon the same factor.

That the tremulous character of voluntary movements shown by patients suffering from paralysis agitans is due to a disturbance of this relative asynchronism seems a reasonable explanation. The suggestions that this phenomenon of dynamic tremor or step-like contraction and relaxation is due to intermittency of voluntary effort, to faulty and intermittent relaxation of movement antagonists or to the disturbing effect of some hypothetical "tremor centre," are all extremely unsatisfactory. The steppage of voluntary movement occurs at a rate which is far higher than that which might be explained in terms of spasmodic voluntary effort. Defective relaxation of the antagonists, even if otherwise satisfactory as an explanation, could apply only to disturbances of limb movements in which shortening and lengthening, or vice versa, respectively of the two muscle groups were permitted, whereas we know that intermittency of effect is more readily observed under conditions of isometric activity. Further, this explanation of faulty relaxation of antagonists argues a defect of co-ordination and reciprocal innervation which is not shown in any other conditions of movement and must be arbitrarily held to be restricted to the mutual relations of muscles acting in opposition upon the same limb segment. Moreover, the graphical records show that during, for example, active flexion and extension of the elbow against a constant force tending to cause extension, the tremulous character of the movement record is present both during contraction and during relaxation of the flexors, and that where any obvious difference in the degree of this dynamic tremor is present (apart from the sudden temporary yield which occurs at the switch-over from contraction to relaxation) it is better marked during relaxation than during contraction. If the steppage of active contractions is to be explained as due to defective co-ordination between the flexors and extensors and allied to the motor perseveration with fixed retention of posture seen elsewhere in these patients, it would be expected that in the above circumstances flexion would be much more tremulous than extension. For during flexion the retention of shortening in the extensors would considerably hamper the efforts of the flexors, while during extension the tendency of the triceps to remain lengthened could not possibly affect the smoothness of this movement which is dependent entirely upon relaxation of the flexors yielding to the constant passive force tending to produce extension.

The implication of some hypothetical tremor centre as being responsible for both the static tremor and dynamic tremor of voluntary movements bears no relation to the observed facts and introduces an unnecessary complication.

Since the earliest description of the static tremor of paralysis agitans it has been recognized that this characteristically disappears temporarily when the relative position of the limb segments is altered and reappears when they are again relatively fixed—this reappearance does not take place at once, but only after a short period of quiescence, after which it increases to its original degree.

This observation is clearly allied to the results of electrical recording here reported, inasmuch as the volleying of action current discharge which is seen at any one degree of maintained tension disappears as the tension is increased and reappears when the tension is again kept constant at another level, i.e., the volleying is either only present, or if otherwise present is maximal when the total activation of the muscle is constant, and absent or minimal when it is changing.

It is noteworthy that this transitory asynchronism which accompanies changes of tension in the muscle and which contrasts with the abnormal synchronism associated with maintained contractions, is characteristic of changes made in the directions of increase and not of decrease of activity.

This suggests that while the tension is increasing new units are thrown into activity in the normal way, i.e., out of phase with those already in operation, that when the tension is kept constant the impulses tend to be thrown into progressive synchronism, and that during decrease of the tension the volleying of impulses does not disappear in the same way as during its increase because the activated groups are allowed to fall out of activity as groups, i.e., the individual units are not dissected out from the groups into which they have been thrown and allowed to become inactive separately. If this be so, then the fact that increase of tension is achieved through the activation of further units, while decrease of tension is brought about by the successive damping down of synchronous groups, accounts for the observations recorded above that the shortening of a muscle in opposition to a constant force is more smooth than its lengthening when yielding to the same force.

Some degree of synchronism of motor units is normal in healthy subjects under certain conditions which have been detailed above. Higher degrees of synchronism appear under maximal voluntary effort, when these are sustained for a period which leads to rapid fatigue. Complete synchronism is only found in the tendon reflexes (fig. 14) and in the muscle-twitch artificially evoked by electrical stimulation of the muscle at its motor point.

Patients suffering from paralysis agitans show a tendency towards abnormally high degrees of synchronism of the voluntarily activated motor units. This provides the difficulty in grading fine or slow movements and the difficulty in maintaining constant tensions seen in such cases. It has been shown that involuntary tremor is associated with a volleying discharge of motor units of the same type as that shown in voluntary movements.

To Professor Adrian, who very kindly advised me in the setting up of the apparatus and of whose work this is an application, my sincere thanks are due. I have also to thank the physicians of University College Hospital and of the Hospital for Epilepsy and Paralysis, Maida Vale, for allowing me to have free access to their cases of Paralysis Agitans for the purpose of this investigation.

REFERENCES.

[1] ADRIAN, E. D. and BRONK. *Journ. of Physiol.*, 1929, **67**, 120.
[2] MATTHEWS, B. W. C. *Ibid.*, 1928, **65**, 225.
[3] SCHAFER. "Textbook of Physiol.," Edinburgh, 1900, **11**, 207.
[4] WALSHE, F. M. R. Oliver Sharpey Lectures, *Lancet*, 1929, **1**, 1024.

LEGENDS TO FIGURES.—PLATES XXV-XXVIII.

FIG. 4.—Records taken electrically from the right triceps muscle of a woman suffering from paralysis agitans. The arm is being fully supported and relaxed as much as possible. Tremor was easily visible at the rate of 100 beats in 18 secs. The time marker (below) records 1/100 secs.

FIG. 5.—Record taken from the right triceps muscle of a healthy normal subject, during a minimal voluntary extension effort controlled by the loud-speaker sounds. Time intervals (below) 1/100 secs.

FIG 6.—Three records taken from the same healthy normal subject as in fig 5. They show three stages in the steady increase of active contraction. Time marker below 1/100 secs.

FIG. 7.—Record taken from the right triceps muscle of the same subject as in fig 5 and 6 during maximum efforts to maintain the tensometer spring as fully deformed as possible.

FIG. 8.—Record taken from the right triceps muscle of a man suffering from paralysis agitans during his effort to maintain a steady active contraction of minimal force.

FIG. 9.—Record from a Parkinsonian patient. During the early part of the record the patient was maintaining a steady contraction equivalent to a push against the tensometer of 3 kgm. This was then gradually increased to a push of 5 kgm and again kept constant at this level. It shows that the volleying present at the lower level of steady tension disappeared during the stage of increasing tension and reappeared when it was again kept constant at a higher level.

FIG. 10.—Reproductions of graphical and electrical records obtained simultaneously from a rabbit. The electrical records were those from a needle electrode pushed into the right soleus muscle. The graphical records were obtained from an isometric torsion spring myograph connected to the tendo Achillis detached from its insertion. The graphical records marked 1, 2, 3, 4 contain each three lines. The lowest indicates break shocks supplied to the exposed right sciatic nerve-trunk from an induction coil. The middle line indicates time intervals of 1/5 sec. The uppermost line is the myographic record. The rate of stimulation was increased by steps from records 1 to 4 being constant throughout any one record.

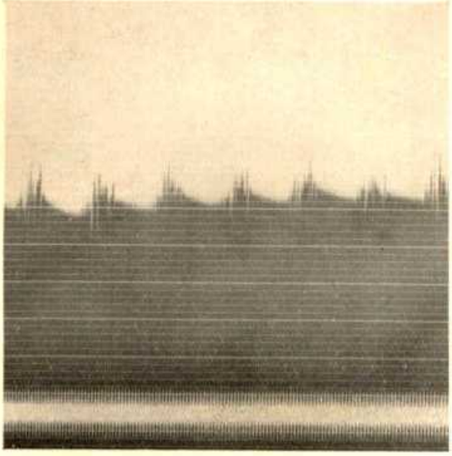


FIG. 4.

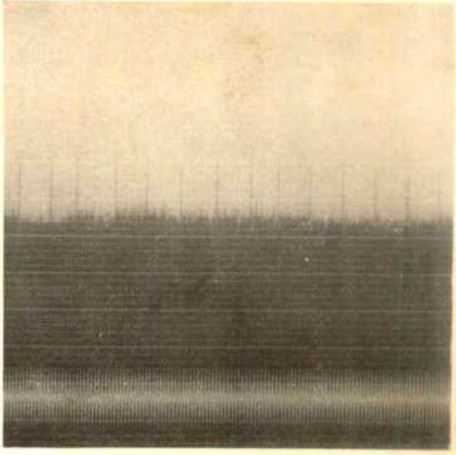


FIG. 5.

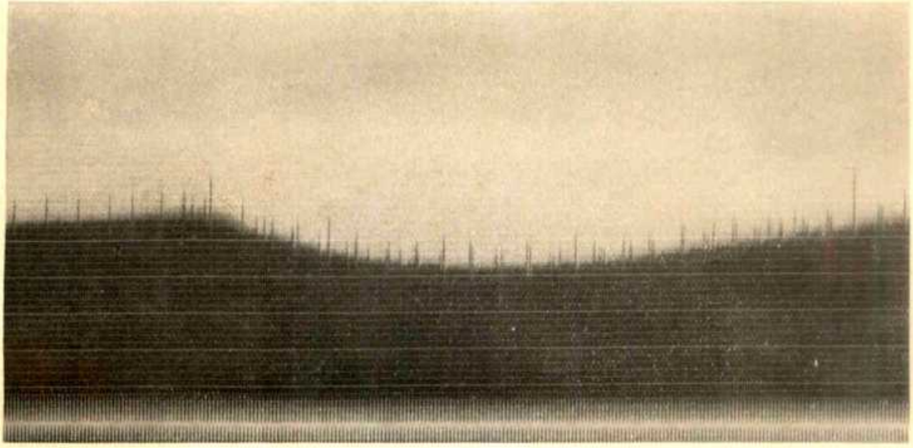


FIG. 6a.

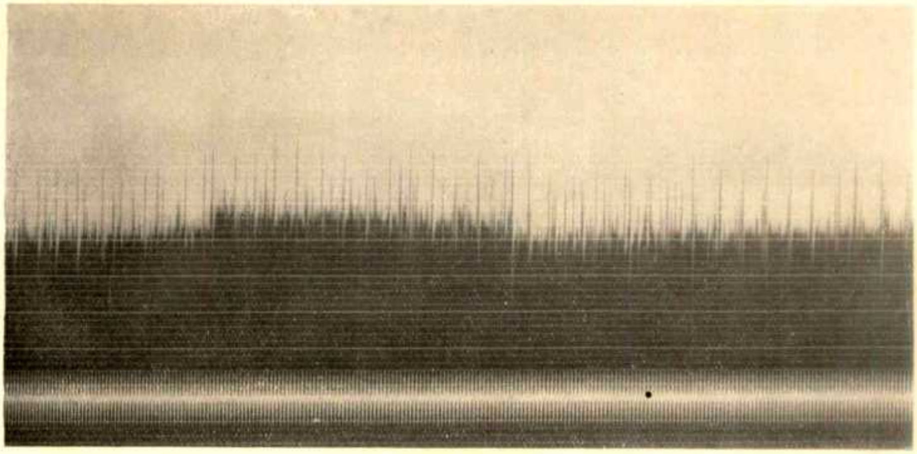


FIG. 6b.

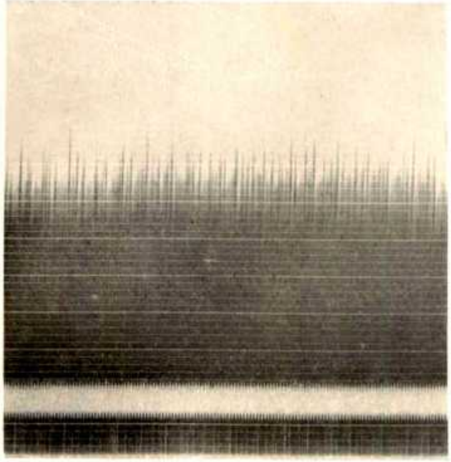


FIG. 6c.

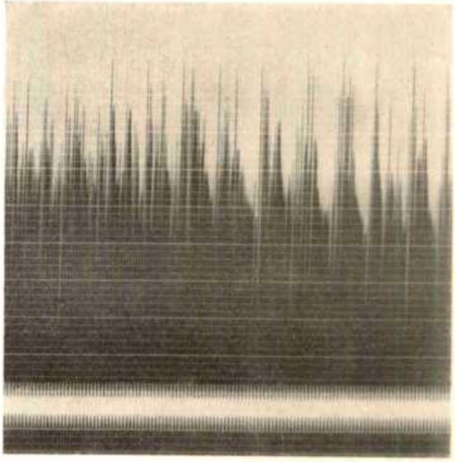


FIG. 7.

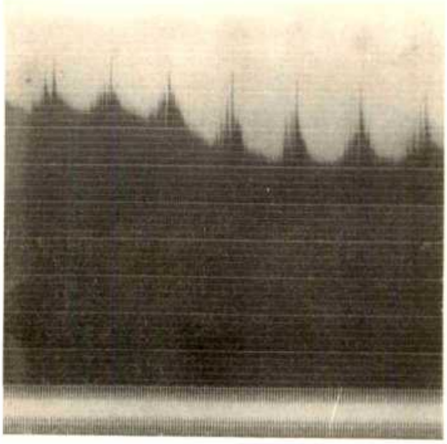


FIG. 8.

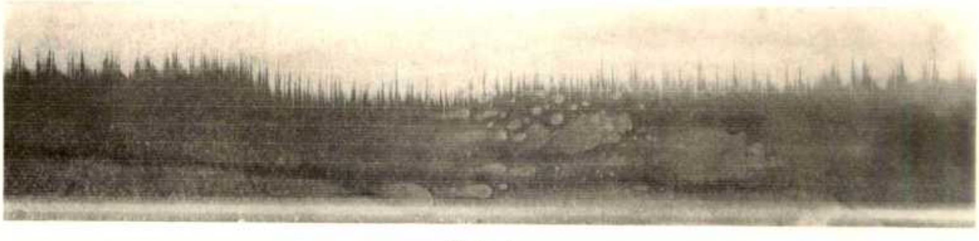


FIG. 9.

PLATE XXVII.

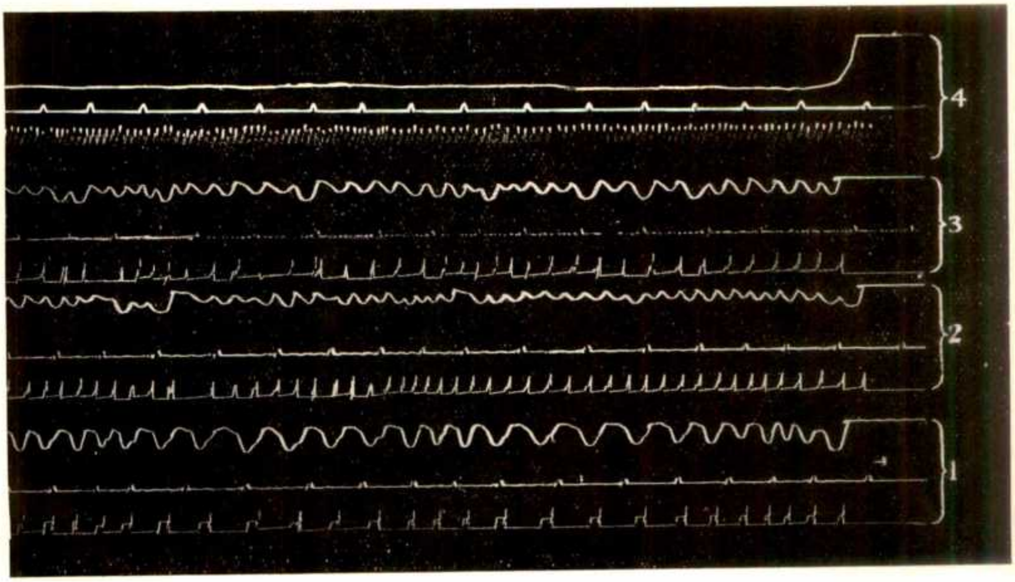


Fig. 10*a*.

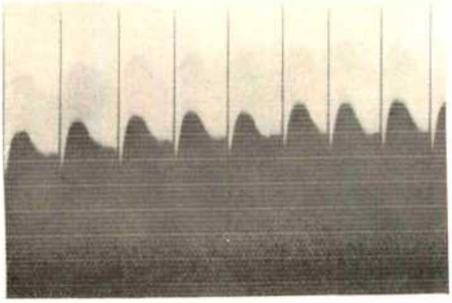


Fig. 10*b*.

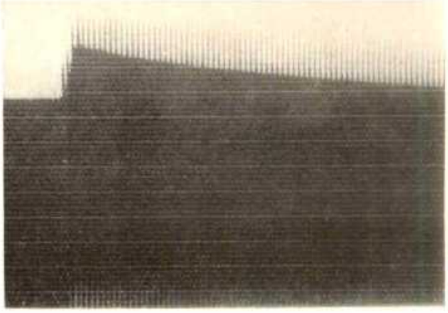


Fig. 10*c*.

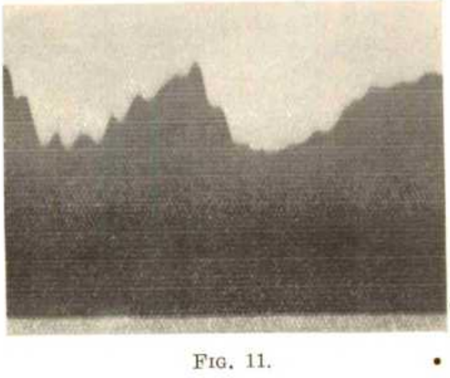


Fig. 11.

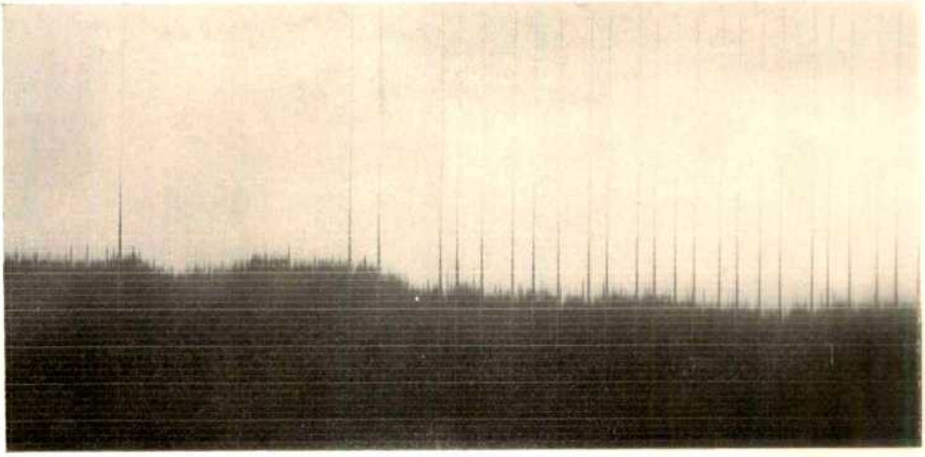


FIG. 12.

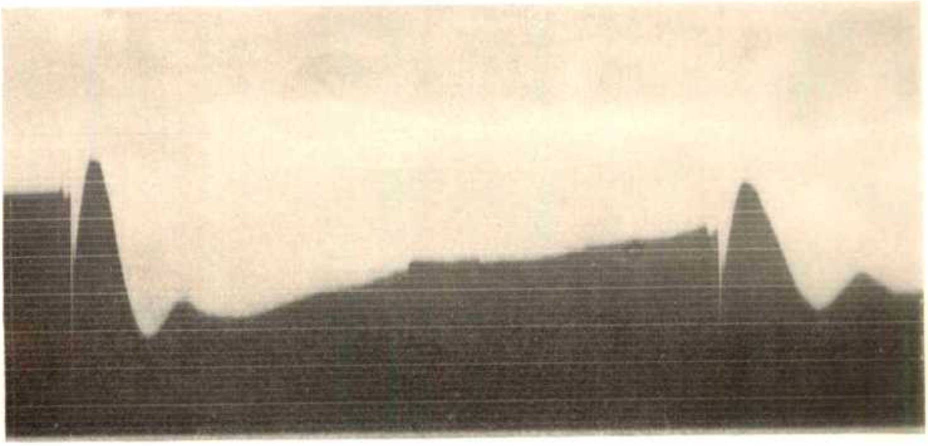


FIG. 13*a*.

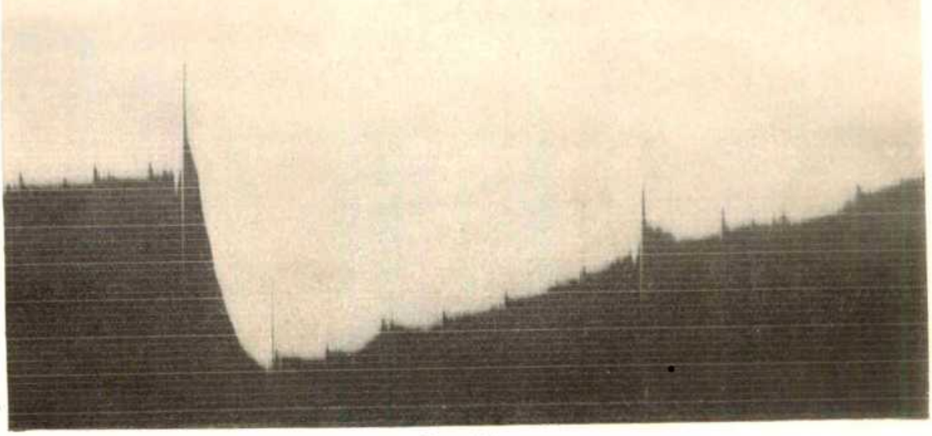


FIG. 13*b*.

The electrical records accompanying these bear the same numbers as the graphical records to which they correspond. It will be noticed that at low frequency each stimulus gives rise to a contraction-relaxation wave in the graphical record, and an action current deflection followed by a shift of the base line due to slight muscle shortening, in the electrical record. At high frequency the graphical contractions have fused into a tetanus without relaxation. but each stimulus is still followed by an action current in the steadily contracted muscle.

FIG. 11.—Record taken from the triceps muscle of a patient with paralysis agitans. The arm was fully supported and complete voluntary relaxation requested. Passive flexion and extension of the elbow gave rise to the gross shifts of the base line here recorded, in which is seen the cogwheel type of resistance to such passive movements.

FIG. 12.—Record taken from the triceps muscle of a normal healthy person during slight voluntary contraction effort. The muscle showed fibrillation of that part of its substance impaled by the needle. The very large deflections seen on this record occurred simultaneously with visible local fibrillation of the muscle.

FIG. 13.—Records taken from the soleus muscle of a patient suffering from paralysis agitans. During the upper record voluntary relaxation was complete—during the lower record a slight contraction effort was being made. The tendo Achillis was tapped with a tendon hammer twice during each record. The upper record shows the sudden action current. This followed a slight downward deflection of the base line due to the tap and was followed by the grosser changes due to the muscle shortening. The lower record shows two large action currents each preceded by a downward shift of the base line due to the tap on the tendon. Each sudden synchronisation of the action currents provided by the tendon reflex is followed by a short period of inhibition. The first gave rise to a visible reflex contraction, and some activity rebound is seen upon the record. The second did not set up any visible reflex contraction but the action current, the inhibition and the slight rebound are all present.

Proceedings of the Section of Neurology of the Royal Society of Medicine.

President—Dr. GORDON HOLMES, C.M.G.

Clinical Meeting held at the National Hospital, Queen Square, W.C.1, on Thursday, November 14.

Chronic Abscess of the Spinal Cord.

By MACDONALD CRITCHLEY.

FEMALE, aged 18. Two and a half years ago had a septic arm requiring three operations. Four weeks afterwards had an attack of headache, backache, vomiting and fever, lasting about thirty-six hours. From this time similar attacks recurred with great regularity every nine days. Six months later was admitted to a general hospital where she remained under observation for over six months. A tentative diagnosis of rat-bite fever was made. The attacks gradually decreased until Easter, 1929, when after a particularly severe bout the legs became weak. This was actually the last febrile attack, but weakness of the legs persisted and grew progressively worse. Gradually numbness of the lower limbs, constant pain in the back and loss of sphincter control developed. On examination—spastic paralegia with sensory loss, up to level of sixth thoracic segment. X-ray examination of spine revealed no abnormality; lipiodol was held up between the fifth and sixth dorsal bodies. Cerebro-spinal fluid showed a well-marked loculation syndrome.

Operation, August 2, 1929 (Sir Percy Sargent).—Mid-dorsal laminectomy; in the region of the seventh dorsal spine the dura was greatly thickened. When this was incised, a mass was discovered lying outside the cord, especially on its left lateral aspect. Portions of the mass and of the overlying dura were removed for investigation. Histological examination revealed that the mass was composed of highly vascularized granulation tissue containing numerous staphylococci. The dura contained abundant infiltrations of plasma cells.

For the first three weeks after the operation there was a purulent discharge from the wound, which afterwards ceased altogether. There has been some return of movement and sensation to the legs and an obvious improvement in the general health.

Dr. P. CLOAKE said he was not convinced there was any relation between the original infection of the patient's arm and the condition found at operation, especially in view of the fact that the local infection preceded the devolopment of spinal symptoms by two years. It appeared to him more probable that if the granulation tissue removed at operation was inflammatory it was due to infection from some other source.

Dr. A. FEILING asked if any evidence of osteomyelitis of the vertebral column was found at the operation or in the X-ray plates. If the lesion found was inflammatory it appeared to him that it would most probably have spread from the neighbouring bone.

Dr. J. G. GREENFIELD said that staphylococci could be easily demonstrated in the tissue removed by the surgeon. This was a type of chronic granulation tissue and its slow growth could be naturally explained by an infection of low virulence. In view of the histological nature of the tissue it seemed to him quite probable that it had been present for a long period and had developed slowly.

Dr. G. HOLMES suggested that although the condition described was not an abscess of the spinal cord, the failure of more marked improvement by operation after removal of the compressing tissue suggested the possibility of chronic intramedullary infection too. He referred to cases published by Chiasi, Collier and Turner, and others, and pointed out that in typical cases of spinal abscess the symptoms developed rapidly and nearly always led to an early fatal termination.

Dr. CRITCHLEY referred to the rarity of spinal abscesses; in 1926, Adson and Woltman were able to collect twenty-nine cases from the literature, to which they added a personal case. All but two proved fatal. The history in the present case was unusually long, the longest history in the literature being seven months.

Progressive Ataxia in a Child associated with a Positive Blood Wassermann Reaction.

By D. DENNY-BROWN.

G. B., male, aged 4 years and 2 months, admitted to hospital for unsteadiness in gait, which had been first noticed eighteen months ago, and had slowly and gradually progressed, and unsteadiness in the arms, which had been first noticed twelve months ago and had gradually progressed.

He was an only child, the parents married five and a half years ago. There were no other pregnancies. Labour was not prolonged and forceps was not used. Breast fed. Perfectly healthy at birth and after, except for two attacks of "influenza," once two years ago, and once eighteen months ago (his mother also had influenza on each occasion). In each of these attacks he was irritable and feverish and vomited several times, but no other symptom was noticed. No convulsions had occurred. He was not late in learning to walk or to talk, and his gait was perfectly normal until the age of 2½, when the unsteadiness was first noticed when he was chasing a dog on a garden lawn. He began to lisp slightly in speech about six months ago, but the lisp has not increased.

A month ago he said that his knees and toes ached, he was a little feverish (100° F.) and began to cough occasionally. The pains ceased the same afternoon and have not recurred. The cough continued up to the time of admission and he occasionally said his throat felt sore.

No history of any similar complaint, or of deaths in infancy.

Physical examination.—Bright, intelligent child, with head a little larger than normal. No stigmata of congenital syphilis. Colour good. Speech occasionally slightly lisping. Well behaved, clean in habits. Occasional dry cough with salivation. No defect in visual acuity and no defect in the fields can be demonstrated. Slight pallor of both discs, maculæ normal. Pupils react briskly to light. Diplopia on looking to extreme left and slight deficiency in outward movement of left eye. Nystagmus on looking fully to either side, fine and rapid to right, slow and coarse to left. No defect in remaining cranial nerves.

No paralysis or paresis in any limb or trunk movement, but the limbs are all hypotonic and ataxic, with some coarse irregular action tremor in the upper limbs. No wasting. No involuntary movements. Tendon jerks all absent. Abdominal reflexes present and equal on both sides. Plantar reflexes both flexor. No sensory-defect to pin prick, cotton wool, heat and cold could be demonstrated. Gait is extremely ataxic and station very unsteady with eyes open. Nasopharynx inflamed, but no membrane. Culture from throat swab gave chiefly streptococci; no Klebs-Loeffler bacilli; marked reaction to Schick test.

Cerebro-spinal fluid (October 22, 1929) clear, colourless, no cells seen. Total protein 0·025 per cent.; globulin tests, negative. Lange: no change in any tube. Wassermann reaction, negative.

Blood: Wassermann reaction, positive 3,300 (October 22, 1929), test repeated (October 29, 1929) with same result.

Skiagram shows skull of hydrocephalic type but with no other abnormality.

Blood Wassermann reaction of patient's mother is negative; his father is not in England.

Antisyphilitic treatment has so far brought about no improvement.

Dr. G. HOLMES said the chief interest of the case is the origin and the nature of the ataxia. The type of the inco-ordination of movement, the presence of nystagmus, the absence of sensory disturbances and the hypotonia of the limbs, all indicate that the cerebellum is involved, while the size of the child's head and the skiagrams show that a considerable degree of hydrocephalus is present. The pallor of the optic discs may be also due to this. It seems more probable, therefore, that there is a local cerebellar lesion than a diffuse atrophy, and that by interfering with the escape of cerebro-spinal fluid through the fourth ventricle it has caused the hydrocephalus. Though there has been no headache a slowly growing tumour in the vermis of the cerebellum extending into the fourth ventricle is probable; this would also explain the absence of the tendon jerks. Although the Wassermann reaction is positive a syphilitic lesion is improbable, especially as the cerebro-spinal fluid is normal.

Jacksonian Epilepsy provoked by Stimulus to Right Foot or Right Ear.

By D. DENNY BROWN.

A. P., female, aged 51, admitted to hospital on account of attacks of twitching of right side followed by unconsciousness. These attacks first began eight months ago.

She had suffered with no previous illnesses of any kind. Menstruation ceased at age of 48 years. Nothing pertinent in family history.

The first attack occurred in March, 1929. There was sudden unconsciousness without warning, lasting an hour, and followed by general weakness, misty vision and aphasia; gradual recovery set in and was complete in two weeks. Three weeks later she began to have attacks of unconsciousness preceded by twitching in the right hand, giddiness, and a rhythmical "clicking" noise in the top of the head. These fits occurred once a day for a month and then she had treatment in bed for the following month and remained free from attacks.

At the end of May, 1929, she got up again and began to have attacks of unconsciousness whenever anything touched her right ear, or her head just behind the ear (for example, putting her spectacles on). These fits began with a twitching and tingling pain in the right side of the face and a "clicking" noise in the head. The twitching and tingling pain spread to the right hand and arm, and then to the right side and leg. She remained conscious but could not say what she wanted to say during the attack. Weakness and numbness of the right side of the body lasted from one to twelve hours after each attack. The attacks continued on alternate days until July, 1929, when they began to occur each day and were followed by unconsciousness for fifteen or twenty minutes; speech was limited to only one or two words between the attacks and there was some continual weakness of the right arm. She was admitted to Cardiff Infirmary, and the only positive findings were weakness of grasp of the right hand and ten cells per cubic millimetre in the cerebrospinal fluid. An exploration of the left parietal cortex was made (August 29, 1929). The arachnoid had a milky appearance round the superior cerebral veins, and the region of the "supra-angular gyrus" was "very soft" and "brain needles were passed in here but no fluid obtained." The osteoplastic flap was replaced.

The attacks continued (one every two days), and six weeks ago the patient began to see, without warning, a blue light immediately in front of her eyes. This occurred at intervals of two to three days, and lasted twenty minutes each time. The light came and went rhythmically with the frequency of the pulse, and had no relationship to the time of occurrence of other phenomena.

Also six weeks ago she began to have attacks of unconsciousness, brought on by some particular stimulus to the right foot or the right leg below the knee, for example pulling a stocking over this foot. These attacks also began with clicking in the head and a tingling pain and twitching starting in the right foot and passing up the right leg, and down the right arm and to the face. They were followed by unconsciousness for a few minutes and by residual numbness, aphasia and increased weakness of right limbs for an hour or two.

For a month one or other kind of attack occurred every day, and she was afraid to touch her right ear and right foot. Once an attack was provoked no further attack was caused by touching either of these parts until about twenty-four hours had passed, and then some chance movement with contact at one or other part excited another attack.

During the last fortnight the attacks have been fewer, and she had not had one for a week previous to admission, in spite of frequent stimuli to the "sensitive" parts. Since August, 1929, she had had occasional double vision when looking to the right, lasting an hour or so. Has had frequent difficulty in remembering the names of things, and her husband's name for the last two months. She has not been able to write intelligibly since the beginning of August. She has often lately seen a large shadowy figure to her right side, but it is not there when she looks round, and she has not seen it when she looks forward again.

Physical examination.—Slight dysarthria of lingual type. Visual acuity $\frac{6}{12}$ right and left. No field defect to white or colours. Disc edges are clear, their colour is good, and the vessels of normal appearance. Variable rapid nystagmus occurs on looking to right, and slow jerks on looking to left. Hypalgesia to pin-prick over right face. Other sensations unaffected. Corneal reflexes are brisk and equal. Right palpebral fissure is wider than the left and there is weakness of the right side of her face. Palate moves slightly to left on articulation. Tongue is protruded to right. Occasionally very fine rapid tremor is present in her left hand, but there is no weakness, change in tone, or inco-ordination in either upper limb or either lower limb. Tendon reflexes are all present and equal on the two sides. The left plantar response is flexor, the right less definitely flexor, but not extensor. The abdominal reflexes are absent on both sides.

There is hypæsthesia to pin-prick and cotton wool over the whole right side, but no inaccuracy to heat and cold, no astereognosis, and two-point discrimination is equally accurate in both sides.

No bruit can be heard over any part of skull. Blood-pressure is 115/70. Gait is normal.

Cerebrospinal fluid: pressure 190 mm., three cells per cubic millimetre. Total protein 0·065 per cent., globulin tests negative. Lange, no change; Wassermann reaction, negative in cerebrospinal fluid and in blood.

Skiagrams show no calcification within skull.

Two attacks have been observed, each brought on by stimulus to the right foot, one on October 26, 1929, and one on October 31—stimulation of right foot and right ear on each other day has not provoked an attack. The first attack was produced by eliciting the knee-kerk on the right side, the second by pulling the bedclothes away from the right leg. Both attacks began by tonic extension followed by twitching of the right ankle, knee and hip and then of the right arm, the right side of her face and immediately following this of the whole left side at once. The pupils were inactive, no bruit was heard over the skull, and no plantar responses were obtained (great toe tonically flexed). Duration of unconsciousness about four minutes, followed by aphasia and then marked perseveration, with weakness of the right arm and leg and an extensor response on right side. Complete recovery was attained three hours after onset of the attack, with return of all signs to those found on admission.

Dr. GORDON HOLMES referred to cases he had described in which local epileptic attacks were similarly provoked by peripheral stimuli. During the investigation of the disturbances of sensation produced by cortical lesions he frequently found that the repeated or prolonged application of tactile or other stimuli excited local epileptic phenomena in the part stimulated, if a lesion existed in the proximity of the motor or sensory representation of this part in the cerebral cortex. These phenomena generally were clonic movements which usually spread in the manner of an ordinary Jacksonian attack, but occasionally they consisted of a numbness or tingling of the part stimulated, which often spread in the same way, or the part stimulated might become numb or "dead" and so anæsthetic that further investigation was impossible. One of his patients, a man with a gunshot wound in the region of the motor cortex of the left hemisphere, asserted that the continued use of his right hand, as in the employment of carpenter's tools, would bring on an epileptic attack starting in the hand.

He has also observed men with lesions in the neighbourhood of the visual cortex, and subject to attacks of visual epilepsy, in whom epileptic visual phenomena were apparently brought on by a strong light stimulus, as a visit to a cinema. And he has seen patients with lesions, traumatic and neoplastic, in the neighbourhood of the auditory centre in whom epileptic attacks followed exposure to loud noises. All these cases are clearly parallel to that shown by Dr. Denny-Brown. On the other hand we have the converse in the well-known fact that a ligature around the limb, firm grasping of the convulsed part, or passive arrest of the spasms, may prevent the spread of a Jacksonian attack.

Dr. C. P. SYMONDS referred to one case in which epileptic attacks were easily excited by music, and especially by the sounds of brass instruments, and to a second patient subject to epileptic attacks commencing with spasms of his left toes in which description of an attack, or focusing of attention on its symptoms, would bring on a seizure.

Dr. R. IRONSIDE described the case of a patient in whom generalized epileptic seizures were provoked by music, and especially when he played the piano.

Dr. DENNY-BROWN, in reply, pointed out that as far as he is aware acustico-motor epilepsy is excited by unexpected sounds only. In the case he has presented the element of surprise is not a necessary factor. In his opinion it is impossible in the present state of our knowledge to determine the mechanisms concerned inthe production of an attack by peripheral stimuli.

Pituitary Tumour, with Goitre and Acromegaly.

By REDVERS IRONSIDE.

J. B., female, aged 60. Twenty-five years ago she began to take larger shoes and gloves and noticed a swelling appearing in the neck. Fifteen years ago, a retrosternal goitre was partially removed on account of breathlessness, with residual paralysis of the left recurrent laryngeal nerve. The patient has complained of headache, which has not been severe during the past year. No giddiness, faints or vomiting.

On examination.—Typical acromegalic appearance with hypertrophic changes in the interphalangeal and elbow joints. Hard swelling in the region of the thyroid. Fields of vision bi-temporally constricted to red and green, but not to white. Skiagram of sella turcica shows considerable enlargement. Shotty glands in both supraclavicular regions. Symmetrical enlargement of submaxillary glands. Hæmorrhages in both fundi. Blood-pressure, 220/165. Urine contained a trace of albumin, but no sugar.

Dr. P. CLOAKE referred to a similar case in which during life obstinate constipation was a prominent symptom, and after death there was found an enormous enlargement of the bowels. He raised the question as to whether a defect or disturbance of pituitary secretion was responsible for the fæcal stagnation. He described another case of acromegaly in which during the course of deep X-ray applications to the pituitary a goitre developed.

Spinal Caries with Compression Paraplegia.

By HUGH G. GARLAND.

T. B., male, aged 62. Admitted to hospital, July 17, 1929, complaining of pain encircling the trunk at the level of the umbilicus of eighteen months' duration. It is increased on coughing or sneezing. Six months ago weakness of the legs developed rapidly with incontinence of urine and fæces; three weeks later sphincter control returned and has been normal since. There has been numbness in both legs for two months and occasional flexor spasms. General health is very good. He had a urethral discharge at age of 25 (untreated).

Physical examination.—Some weakness of both legs with symmetrical muscular wasting and a mild degree of spasticity. Weakness of lower half of rectus abdominis. Hypalgesia over legs and lower trunk, with impairment of temperature and vibration sensibility over the same area. Upper border of sensory loss is at level of umbilicus. Gait slightly spastic. Knee-jerks exaggerated: bilateral knee and ankle clonus and extensor plantar responses.

Prominent veins over upper part of chest. Dullness to percussion in front at inner end of second left intercostal space and to right of eighth and ninth dorsal spines over an area about 4 in. in diameter, with diminished air entry over same area. Marked prominence of eighth dorsal spine and of ninth rib on each side. Second aortic sound accentuated. Blood-pressure 174/108 mm.

Second examination.—X-rays: ninth dorsal vertebra is evenly collapsed; intervertebral discs and the vertebral bodies above and below are normal. An opacity, roughly circular in outline and 4 in. diameter, extends to the right of the collapsed vertebra and shows central patchy calcification. There is bulging of the descending arch of the aorta and continuous with this below is the convex shadow of the descending aorta which is displaced or dilated. Old fracture of eighth and ninth left ribs.

Cerebrospinal fluid: Pressure 100 mm., with no rise on jugular compression. Slightly yellow fluid; 2 cells per c.mm.; protein, 0·18 per cent.; Lange curve, negative; Wassermann reaction, negative.

Blood: Wassermann reaction 4444. Sedimentation rate normal.

Tuberculin skin test negative.

After a course of novarsenobillon, mercury, bismuth and potassium iodide, the blood Wassermann reaction, the general condition, and the cerebrospinal fluid are unchanged.

The lesion is regarded as inflammatory rather than neoplastic. The fact that the lungs have not been invaded is in favour of this view. The escape of the intervertebral disc shows that the process is not tubercular.

Dr. A. FEILING suggested that the radiographic appearances were in favour of a chronic abscess, which possibly commenced in an osteomyelitis.

Dr. C. P. SYMONDS said that despite the clear-cut shadow seen in the skiagrams there could be, in his opinion, little doubt that the primary lesion was neoplastic, possibly a sarcoma which often runs a chronic course. The involvement of the ribs is also in favour of this. He thought, however, that the possibility of hydatic disease should be considered.

Dr. J. P. MARTIN considered that though the symptoms have not advanced during the last three months, a new growth was the most probable diagnosis. He agreed that though the blood Wassermann reaction is positive the lesion is not syphilitic, though he recalled that Gowers had described paravertebral syphilitic masses.

Polyneuritis Cranialis.

By REDVERS IRONSIDE.

W. R., aged 18, a car-boy. Admitted to Guy's Hospital, under Dr. Poulton, August 8, 1929, on account of gradually oncoming right ptosis, noticed a fortnight before. Patient had felt in his usual health and pulse and temperature had been normal. Within the past week he had noticed numbness over the right eye.

On examination.—A pale, spare youth, with complete right ptosis. Optic discs, visual acuity and fields of vision, normal. Right pupil larger than left, and reacts very sluggishly to light and on convergence. Left pupil normal. Complete external ophthalmoplegia, except for some power remaining in the left external rectus. Sensory loss to pin-prick and cotton wool over first division of right fifth. Complete palsy of the right side of the face, upper and lower. Other cranial nerves normal. No deafness or otorrhœa. No sensory, motor or reflex abnormality. Urine normal. No glands palpable in neck. Spleen not enlarged.

Cerebrospinal fluid: eight cells per cubic millimetre; albumin, 0·04 per cent.; globulin positive; Wassermann reaction negative. Blood-pressure 110 mm., Wassermann reaction negative.

This patient has never suffered from headaches or vomiting. Gradual recovery has been taking place. The pupils are now equal, central and circular and react to light directly and consensually, and on convergence. Slight weakness of both external recti remains. There is slight right ptosis and hyperæsthesia to cotton wool and pin-prick over the first division of the right fifth. Corneal reflexes brisk and equal. Slight right peripheral facial weakness. Other cranial nerves normal. No sensory, motor, or reflex abnormalities in the trunk or limbs. The case is presented for discussion and pathological diagnosis.

Lesion of Third, Fourth, Fifth and Sixth Left Cranial Nerves.

By LEWIS R. YEALLAND.

W. C., female, aged 27, in October, 1928, began to see double in artificial light. In February, 1929, diplopia became more or less constant and her left eyelid began to fall. In July the ptosis became complete and in addition she complained of stiffness and neuralgic pains in her left face and loss of the sense of taste and of smell on the left side. The symptoms have been gradually progressive except in January and June, when there was, on both occasions, definite improvement for about a fortnight.

Physical examination.—Optic discs and fields normal. Left eye presents ptosis, internal and external ophthalmoplegia and proptosis. When the eyes are at rest a small portion of sclera is visible between the left eye and its external canthus. On attempted conjugate deviation to the right, the left shows inhibition. Inability to deviate jaw to right; wasting of left temporal muscle and weakness of left masseter. Left corneal reflex absent; loss of sensation to pin-prick and heat and cold over all divisions of left trigeminal nerve. A sensation of a "small burn" is evoked on some contacts by pin-prick but not by thermal stimuli. Sense of taste lost throughout left side of tongue. On tests, the sensation of smell appears to be normal, although the patient is conscious of some defect. Examination of other cranial nerves showed no defect. Reflexes: right plantar is indefinite, otherwise the reflexes are normal. The blood, cerebrospinal fluid, blood-sugar and skiagram of skull showed nothing pathological.

Dr. R. IRONSIDE confessed he was mystified as to the nature of the lesion in his case. Unilateral symptoms, as those in Dr. Yealland's case, are often due to a tumour at the base of the brain, but the absence of headache argued against this diagnosis in this case. He suggested the nerves might be compressed by an aneurysm of the internal carotid artery.

Dr. W. J. ADIE agreed that an intracranial aneurysm was the most probable diagnosis in Dr. Yealland's case. He had recently seen similar symptoms in a patient who died shortly afterwards with apoplexy, the symptoms of which suggested rupture of an aneurysm.

Dr. WORSTER-DROUGHT did not think a tumour could be excluded. He described the case of a patient with the same signs in whom the ocular palsies had existed for seven years before headache appeared. The patient later developed papillœdema and at operation a large tumour was found in the middle fossa of the skull.

Dr. REES referred to a case recently in the Hospital under the care of Dr. Gordon Holmes. He developed gradually eleven years ago a complete internal and external ophthalmoplegia of the left eye, with pain and later anæsthesia in the distribution of the ophthalmic division of the trigeminal nerve. Ten years later his left eye became blind and slightly proptosed, and he began to suffer with slight headaches. Radiographs revealed a large partly calcified tumour, probably a psammoma, in the floor of the middle fossa of the skull. This case shows that headaches may be a late symptom in tumours of this region.

Sudden Paralysis in the Left Lower Limb, Associated with Hæmophilia.

By H. J. SEDDON.

S. L., male, aged 24, chauffeur.

History of present condition.—June 9, 1928: The patient was involved in a motor-car accident and admitted to Kingston Hospital. He was unconscious for three days as the result of "concussion." X-ray examination of spine showed fracture in region of third and fourth lumbar vertebræ; there was some injury to the right ankle, but apparently no bony lesion.

He remained on his back for four months, and returned to work six months after the accident—not wearing any form of spinal support. After the accident patient noticed that he occasionally lost control of his legs and fell. There was no paralysis and no loss of consciousness.

Early in 1929, he stumbled and injured right hip. A large swelling appeared in upper and outer part of thigh, but a skiagram did not show any fracture of femur and the swelling gradually disappeared.

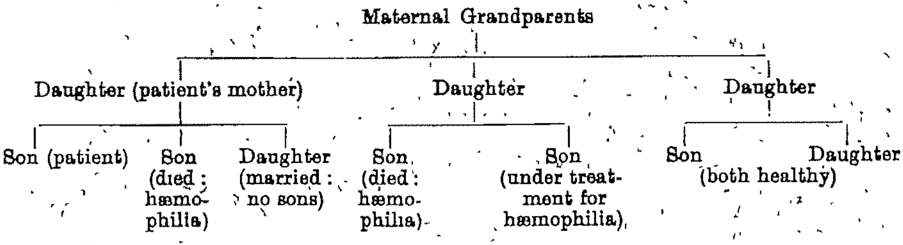
In May, 1929, his right ankle "gave way" and patient was admitted to hospital with a large swelling of that ankle, but again no fracture was found.

In June, 1929, after driving to Portsmouth without accident, became aware of sudden weakness in the left lower limb. The onset was instantaneous and he cannot recall feeling any pain. The paralysis has been substantially the same since.

September, 1929.—"Pins and needles" were sometimes felt in the right lower limb, but there was no muscular weakness of it.

Micturition is normal and the bowels are regular with medicine.

Family history.—The history of hæmophilia is summarized below:—



Past history.—In 1926 patient was admitted to hospital on account of severe hæmaturia and remained there for six months. There were no marked constitutional signs.

On examination.—Cranial nerves normal. In his left leg, the quadriceps extensor muscles are paralysed and no voluntary contraction can be detected in pectineus and adductor magnus. The adductor longus and tensor fasciæ femoris work well. No other muscular weakness found. Sensation: An area roughly corresponding to anterior division of L 3 and 4 in the left lower limb is insensitive to cotton wool, pin-prick and temperature. Vibration of tuning fork not felt on left patella, and only felt poorly at upper and lower ends of the fibula. General diminution in tactile sensibility in the whole of the left lower limb. Elsewhere no sensory changes can be found. Joint sensibility is everywhere normal. Reflexes: biceps, triceps, supinator and ankle-jerks strong and equal on both sides. Right knee-jerk easily obtained, left absent. The abdominal and cremasteric reflexes are normal. The plantar reflexes are flexor. Spine: movements are difficult to observe, but apparently normal. Skiagrams: the earlier skiagrams of spine are not now available: the recent ones show no abnormality of the spine.

Lumbar puncture has not been performed on account of the blood condition.

Dr. A. FEILING said that a local hæmatomyelia had to be considered, though he was not aware that this had been observed in hæmophilia. It appeared to him, however, more probable that the condition was due to compression of the roots by a large hæmorrhage into the psoas muscle.

Dr. J. P. MARTIN had never seen such symptoms produced by a hæmorrhage into the lumbosacral plexus. The absence of severe pain at the onset and the fact that little or no recovery had occurred, seemed to him in favour of a spinal lesion.

Dr. C. P. SYMONDS pointed out how closely the symptoms resemble those produced by a local hæmorrhage into the grey matter of the cord. He had no doubt this is the correct diagnosis in Mr. Seddon's case.

Dysarthria and Abnormal Gait.

By F. PARKES WEBER and O. B. BODE.

The patient, V. A., aged 25, is a strongly-built and well-developed man, who, when sitting at his ease, appears to be perfectly normal. His speech, however, is indistinct, and blurred or husky (not of the "scanning" disseminated sclerosis type), and when speaking he seems to be hampered by a spastic or hypertonic condition of the jaw-muscles. When he walks or when he stands upright (as if to attention) the upper part of his trunk is thrown rigidly back and slightly to the right, and, owing to very slight foot-drop, the left foot is raised somewhat more than the right. When he is speaking, the muscles of his neck and face tend to become spastic. He has a little dysphagia.

Spasm of the right orbicularis muscle seems to have been a prominent feature, but disappeared nearly twelve months ago. There is very slight lateral nystagmus to left. The tongue is protruded somewhat to the right. The patellar and Achilles reflexes are over-active on both sides. There is ankle clonus on the left side, but not definitely on the right. The plantar reflex on the right side is of the normal flexor type, whereas on the left side it either cannot be obtained or a Babinski phenomenon is "indicated." There is no inco-ordination. The maximum circumference of the left calf is 1 cm. less than that of the right calf; the circumference of the left thigh (20 cm. above the upper border of the patella) is 1½ cm. less than that of the right thigh. There is a slight difference at times between the two halves of the face, which may be due to slight muscular hypotonicity on the right side or hypertonicity on the left side.

Nothing abnormal has been noted in the arms, nor in the superficial abdominal reflexes, the pupils, the ophthalmoscopic appearances or sensation. There are no tremors or abnormal choreic or rhythmical movements of any kind. No muscular bradykinesia. No greenish coloration at the corneal margins. Nothing abnormal in the liver, or spleen, or other abdominal or thoracic viscera; nor in the urine, excepting frequently slight excess of urobilinogen. The galactose test of hepatic function gives a negative result, and the blood-serum gives negative Wassermann and Meinicke reactions. The cerebrospinal fluid, when examined at another hospital, was normal and gave a negative Wassermann reaction. The patient seems to be of average intelligence, but perhaps almost abnormally cheerful (slight mental "euphoria"). Nothing abnormal in regard to emotional manifestations (crying, laughing, &c.) has been noted.

The patient is said to have two healthy brothers, and in the *family history* there is nothing abnormal excepting that his father developed right-sided hemiplegia at the age of 28 years, and died of pneumonia at the age of 53 years.

History.— Operation for appendicitis as a boy. Articular rheumatism at 16 years. Suppurative middle-ear disease and mastoid operation five years ago. The patient has always been fond of muscular exercise and can still stand on his hands with ease. In 1924 he had a job as labourer in London (using a sledge-hammer). When this job was over in 1925, he ran thirty-two miles in one day. On the following day he noticed that he was weak in the left foot, and that it tended to hang somewhat, and that in walking he had to raise it higher than the right foot; during the next two years he sometimes used a stick as a support. He thinks that the present illness commenced two and a half years ago with muscular spasms about the right eye, and what he calls "gasping" movements of the mouth. He has had neither the orbicularis muscle spasms nor the "gasping" movements for nearly twelve months. The peculiar gait, dysarthria and slight dysphagia have developed during the last seven months. There is no history to suggest that he has had encephalitis of any kind.

In regard to *diagnosis* we have to consider some degenerative lesion affecting the motor tract, especially to the left leg, together with a superadded functional disturbance; or (2) the possibility of the whole syndrome being functional; or (3) an early and non-typical stage of chronic lenticular degeneration (Wilson's disease).

During demonstration of the case various members pointed out features that indicated a psychogenic rather than an organic origin of the symptoms. Dr. RIDDOCH said that not only does the tongue protrude strongly to the right but that in the mouth it is deviated into the right cheek, a condition not found in organic lingual palsy. Dr. GORDON HOLMES found the left plantar reflex normal, and as the left-sided ankle clonus persisted on strong plantar flexion of the great toe he did not regard it as a sign of organic disease.

Dr. R. D. GILLESPIE said that in his opinion the condition was hysterical. the mode of development of the symptoms was suspicious; no sign was present that could not be imitated; when the patient's attention was diverted the attitude of his trunk was normal, and finally the suggestion to the patient that he could control his symptoms was resented in the manner we commonly find in hysterical subjects.

A Case of Family Periodic Paralysis, with Attacks on Excitement.

By C. P. SYMONDS.

W. F., male, aged 28, locomotive fireman, has been subject to attacks of periodic paralysis since childhood. His younger brother and his mother are subject to similar attacks and the mother's father is said to have had the same complaint. The patient's attacks vary both in severity and duration; one, observed in hospital, lasted for an hour and a half and was of subacute onset. At its height all the voluntary muscles appeared to be affected, but none were completely paralysed. He was, however, quite helpless and inarticulate. All tendon-jerks were abolished. The plantar responses were flexor.

He states that although his attacks may come on without cause they are frequently occasioned by emotion. This may take the form of: (1) excitement, e.g., the cinema, or an exciting moment in a game; (2) fear, e.g., when he receives a summons to go before his superior officer; (3) fluster, e.g., if when doing a job he realizes suddenly that he cannot get it finished in time.

The case is presented as affording a possible link between family periodic paralysis and cataplexy.

Dr. L. R. YEALLAND asked if the faradic excitability of the muscles was affected in the attacks. In a somewhat similar case he had seen he could not, during an attack, produce contraction of the muscles by the faradic current.

Dr. J. P. MARTIN inquired if it were known that in family periodic paralysis excitement brought on attacks of loss of voluntary movement; he could not recall any statement that it did.

Dr. SYMONDS, in reply, said that there had been as yet no opportunity of testing the electrical responses of the muscles during an attack, and that he was not aware that excitement had been previously described as an exciting cause. It is noteworthy that in the patient presented the attacks are not brought on by fatigue, which is the rule in family periodic paralysis.

Arterial Angeioma of Brain.

By C. P. SYMONDS.

G. G., male, aged 44, carpenter, first seen in March, 1929, on account of epileptic attacks dating from the age of 15. The aura consisted of a "wheel of shining blue and silver lights," revolving in a counter-clockwise direction in the right half of the visual fields. As a rule this was followed in one or two minutes by a generalized convulsion. Occasionally a brief vision of "people running about" intervened between the aura of coloured lights and the convulsion. He had been conscious since boyhood of a noise in his head, which he compared to the puffing of a distant railway engine. Recently he had complained of severe headaches and failing vision, and had had an attack of numbness down the whole left side of his body.

On examination.—Showed marked dilatation of the vessels of the scalp, especially over the left parieto-occipital area. A musical bruit simultaneous with the carotid pulse was audible over the whole head, being loudest above and behind the left ear. A skiagram showed grooving of the inner table of the skull by a greatly enlarged and tortuous vessel whose maximal girth corresponds to the left occipital pole. The visual fields showed an incomplete right hemianopia. Early papillœdema was present on both sides. There was bilateral exophthalmos. Both carotid arteries appeared large, and the heart was enlarged 1 in. to the left (confirmed by skiagram).

On April 2, 1929, Mr. Bromley ligatured the left common carotid artery, and the patient has subsequently been subjected to deep X-ray therapy. He has had no fits since the operation. Headache is less and papillœdema has subsided. The bruit, though still audible above and behind the left ear, is less evident both to physician and patient.

Dr. PARKES WEBER pointed out that not only could the pulsations be heard by the patient, but they are audible to the observer if he inserts one end of a rubber tube into the patient's external auditory meatus and the other into his own ear.

Dr. GORDON HOLMES referred to the case of a man, aged 28, who commenced at the age of 16 to have epileptic attacks heralded by a ringing noise in his right ear, and later by the sound of voices, associated with flashes of light in front of his eyes. In each attack he became unconscious quickly and had general convulsions.

Two years ago he began to suffer with headaches in the right temporal and frontal region, and found he could not see fully to his left. Lately the attacks have been preceded by a gustatory aura and a dreamy state. The superficial arteries of his scalp were dilated and pulsated strongly. Papillœdema was present, and the reflexes on his left side were exaggerated, but there was no disturbance of motor or sensory functions. He had a partial left-sided homonymous hemianopia. Sir Percy Sargent exposed the right temporal lobe and found it covered and infiltrated by dilated pulsating vessels. Three deep ligatures were inserted through the temporal lobe and later the right common carotid was ligatured. Since the operation he has had no epileptic seizures, but he still gets dreamy states associated by an unpleasant smell and a curious epigastric sensation. His visual fields have become full.

Pineal Syndrome (Ocular Palsies and Sexual Precocity) in a Boy, aged 10.

By W. J. ADIE.

A. C., aged 12, complains of headache, double vision and shaking of the right arm. His health was very good until he began to have headaches about a year ago; six months later he began to see double and the right arm trembled when he used it. During the last three months he has had several generalized convulsions with unconsciousness. He was "very forward" mentally from the age of 5 years; at the age of 8 years he was "fully developed," and was not allowed to undress before his sisters. His parents are alive and well; he has five sisters and one brother aged 15, all healthy.

His sexual and general development is that of a well-grown youth of 18. Mentally he is intelligent but not precocious; his mother states that he has become dull during the last year. Speech is slow and slightly slurred. Smell, hearing and taste are normal. The optic discs are rather pale but the fields are full and vision is good when his myopia is corrected. When he first came under observation a month ago the pupils were equal and reacted briskly to light but poorly on convergence; upward movement of the eyeballs was absent; all other ocular movements were normal. Now the left pupil does not react to light and the right as it contracts becomes oval. Downward movement is defective in both eyes, but better right than left; lateral movements are good in the right eye, in the left inward, outward and convergent movements are defective. There is no ptosis or nystagmus. Apart from weakness of the left side of the face of lower neurone type, the other cranial nerves are normal.

Power in the right arm is good, but the limb is hypotonic and ataxic; a very coarse tremor, exactly like the intention tremor of disseminate sclerosis, occurs on voluntary movement. The right lower limb is also slightly hypotonic, but there is no tremor and his gait is normal; he stands easily on the left leg alone but cannot do so on the right leg. The power, tone and co-ordination of the limbs on the left side are normal. All tendon jerks are slightly brisker right than left; the abdominal and plantar reflexes are normal. Sensation is normal for all forms except pin-prick, which is slightly diminished on the right limbs and trunk.

Radiological report: A very well developed head, rather like that of an adult. No calcification seen in pineal region. Ventriculograms show a considerable degree of internal hydrocephalus.

Dr. Adie said that the existence of a tumour had not yet been proved. Sir Percy Sargent had incised the brain and opened the right lateral ventricle at the junction of the posterior and descending horns; no tumour was seen or felt. He thought nevertheless that there was a tumour. The lesion was certainly progressive as the ocular palsies had increased under observation; there was certainly a lesion in the mid-brain; did the association of prococity with signs of a mid-brain lesion justify the diagnosis of pineal tumour?

Most cases of pineal tumour were seen in adults; in them there were no sexual changes, but he believed that a tumour of the pineal body in young male children usually, perhaps always, caused precocity. One case of precocity in a female child had been described.

Specimen of Pineal Tumour.

Shown by W. J. ADIE.

The patient, a man aged 21, died a week after coming under observation. His father stated that the illness began four months ago with squint, headaches and vomiting; within a month he was almost blind and unable to stand. The patient said, "I feel all right, but the doctors think there is something wrong with me." He was unable to describe his symptoms and could not give much assistance in the physical examination.

Intense papillœdema was present in both eyes. Vision was reduced to counting fingers at 2 ft. The pupils were large and equal, they reacted slightly on convergence but not to light. Movement of the eyeballs upwards was defective, downwards good, outwards absent, on convergence poor. On looking to the left the right eye made slow, coarse, irregular nystagmoid movements; to the right the left eye made similar but finer and quicker movements. The corneal reflexes were brisk and equal. The jaw deviated to the left side when he opened his mouth. The left side of the face was weak. He was deaf in the left ear, a tuning fork on the vertex was referred to the right ear; the otologist reported he was a bad witness, but that tests suggest a partial lesion of the left eighth nerve. The remaining cranial nerves were normal.

His head was rotated to the right and inclined to the left. The limbs were very weak and flaccid, co-ordination, considering the degree of weakness, was not grossly affected. Sensation was normal. The tendon jerks were very brisk and equal on the two sides. The plantar responses were extensor. He was unable to sit up or stand. He was incontinent of urine and fæces. His physical and sexual development were normal. Dr. Adie said there was no history of precocity in this case.

In view of the severe general symptoms, the character of the nystagmus and the signs of damage to the fifth, sixth, seventh and eighth nerves on the left side, he had expected to find a tumour in the left posterior fossa. He had not attached due importance to the inactive pupils and defective upward movement of the eyeballs in an advanced case like this; if one did not know the order in which the signs had appeared, it was difficult to decide which of them were of localizing value.

Dr. J. G. GREENFIELD described the pathological appearances in the brain. The tumour took origin from the pineal and extended backwards and laterally, infiltrating the tectum of the mid-brain, the posterior commissure and both optic thalami. Its structure was characteristic of a tumour of the pineal body. It contained clusters of large cells with rounded nuclei and one or two long fleshy processes which appeared to run considerable distances from the cell body, for bundles of such processes could be seen with no cell bodies or nuclei in them. The cell clusters or bundles of fibres were separated from each other by fairly wide zones of fibrous tissue in the meshes of which were many lymphocytes. The large cells and their processes had some of the characters of neuroglia cells, but no neuroglia fibrils could be demonstrated in them.

NOTICES OF RECENT PUBLICATIONS.

Handbuch der Neurologie des Ohres. Herausgegeben von G. ALEXANDER, O. MARBURG und H. BRUNNER. II Band. 2te Teil. S. 1228 mit 242 Abbildungen. Berlin und Wien: Urban und Schwarzenberg. 1929. Price 150 Marks.

This volume completes the comprehensive system of the "Neurology of the Ear" which has been issued in several parts by Viennese neurologists and aurists during the past four years. Several articles contained in it are of little immediate interest to neurologists, while some seem a little out of place in a textbook on the nervous disorders of the ear. This does not, however, detract from the value of the system, for the more points that can be made common ground to the neurologist and aurist will prove to be of benefit to both. Stern's long chapter of over 200 pages on the non-suppurative inflammatory lesions of the brain, including encephalitis lethargica, encephalitis, encephalitis associated with other infections, and disseminated sclerosis, for instance, scarcely establishes any relation to diseases of the ear, though it is an admirable monograph on these subjects. Bénesi and Sommer have written exhaustively on the toxic neuritis of the eight nerve, due to various exogenous poisons, or occurring in infections and metabolic diseases. Alexander contributes a series of chapters on the intracranial complications of aural infections, and Brunner deals with abscess of the temporal lobe in an article in which much interesting information on the differential diagnosis of this condition may be found. Syphilis of the eighth nerve and the aural complications of tabes and general paralysis are dealt with more concisely by Schacherl. The aural disturbances that may occur in association with increase of intracranial pressure are described by Fischer, who maintains that there may be a "Stauungsohr" similar in its origin to papillœdema.

To the neurologists the two most interesting chapters are that on disturbances of speech due to lesions of the temporal lobe by Bonvicini, and that on tumours of the temporal lobe by Marburg. The former includes an instructive historical review of the many theories of aphasia, including a very full résumé and a critical appreciation of the work of Head, as well as an objective presentation of the defects of speech produced by local lesions of the brain. Marburg's article is a very valuable contribution to the symptomatology and localization of tumours of the temporal lobe.

The Editors of this textbook must be congratulated on the completion of their enormous task, and deserve the gratitude of both neurologists and aurists for having provided a manual distinguished by the high level of the individual chapters and by the discrimination they have shown in the selection and arrangement of its subject matter.

Brain Mechanism and Intelligence. By K. S. LASHLEY. Pp. 186. Chicago: The University Press. 1929. Price 13s. 6d.

The experiments described by Lashley consist in the training of rats in a variety of motor habits, either before or subsequent to ablation of parts of the cerebral hemispheres, and in the employment of retention tests to ascertain the influence of the lesions so produced upon habits formed either prior to or after the injury.

Lashley finds that the capacity to form the habits tested (maze habit) is reduced by destruction of cerebral tissue in direct proportion to the quantity of tissue destroyed. Equal extent of destruction produces equal degree of retardation in learning, irrespective of the particular cyto-architectural fields involved in the lesion; that is to say, the capacity to learn a habit depends upon the amount of cortex available and not upon its localization or anatomical specialization.

The greater the complexity of the habit under examination, the greater is the retardation in its acquirement after cerebral ablations. Similarly, the capacity to retain a habit is affected in like manner by destruction of cerebral tissue.

From these observations Lashley concludes that the learning process and the retention of habits depend not upon any finely localized structural changes within the cortex, nor upon the laying down of specific functional pathways within it. On the contrary, the mechanism of integration appears to lie in the dynamic relations between the parts of the nervous system rather than upon details of structural differentiation.

In a preliminary chapter Lashley discusses the nature of intelligence, and the relation of the learning capcity to intelligence, and he gives reasons for supposing that the problems of cerebral function in higher animal forms do not differ essentially from those raised in the course of his experiments on rats.

La Syphilis Médullaire. Par LORTAT-JACOB et POUMEAU-DELILLE. Pp. 151. Paris: Masson et Cie. Price 14 francs.

Malaria Provoquée. Par FRIBOURG-BLANC. Pp. 120. Paris: Masson et Cie. Price 15 francs.

These two small volumes form part of a series published under the general title of "Médecine et Chirurgie Pratiques," a title which indicates their purpose and scope accurately. Both volumes have an exhaustive bibliography, but in both, as in so many French publications, a table of contents occupies the place of, and has to do duty for, an index.

Lortat-Jacob and Poumeau-Delille give a clear and comprehensive description of the various syndromes of spinal syphilis, tabes dorsalis not being included in their purview. They deal with their subject under the accepted headings of Ætiology, Pathogenesis, Morbid Anatomy, Symptomatology, Diagnosis and Treatment. The chapters describing the various clinical pictures of spinal syphilis are admirably arranged and are clear and comprehensive, and by themselves would make the volume well worth careful study. In the chapter on Treatment, it is disappointing to find mercury relegated to a minor place, and its indications dismissed in a single line.

Fribourg-Blanc gives a brief historical account of the evolution of malarial therapy. His descriptions of the practical details of this mode of treatment, of its course and complications, of its indications and results are excellent, and he has produced a volume that may be unreservedly recommended.

Die Encephalitis lethargica : ihre Nachkrankheiten und ihre Behandlung. Von C. v. ECONOMO. S. 251. Berlin und Wien: Urban und Schwarzenberg. 1929. Price 20 Marks.

Here we are presented by Economo, who first recognized and described the disease, with a clinical and pathological study of encephalitis lethargica based on his own experiences. The literature of the subject is not neglected, but his pages are happily not overburdened with references to articles that have added little to our knowledge or can claim recognition only on the grounds of priority. The history of the first outbreak of the disease in Vienna and of its spread over the world is particularly interesting, and so too is the critical study of earlier epidemics which may have been identical with or allied to it. The ætiology and epidemiology are fully discussed, and the symptoms of both its acute and chronic stages are described in considerable detail. The chapters on the pathological anatomy of encephalitis lethargica and of its sequels are excellent and concise, but more illustrations would have been useful to the student. As many other Continental authorities, the author emphasizes the value of intravenous injections of iodide combined with vaccineurin in the treatment of the acute stages, but he adds little to our ordinary therapy of the later complications of the disease. The final chapters on what encephalitis lethargica has taught us of the functions of the nervous system is particularly instructive and interesting,

Mental Deficiency. By A. F. TREDGOLD. Fifth edition. Pp. 535. London; Baillière, Tindall and Cox. 1929. Price 25s.

This book first appeared twenty-one years ago, and the four editions which have been published since then indicate how useful it has proved itself to be to students and practitioners. In the present edition numerous alterations have been made, some of them necessitated by recent legislation, and most of the chapters have been revised, but the original arrangement and classification is closely adhered to. The treatment and legal status of the mentally defective are carefully dealt with.

Principles of Experimental Psychology. By H. PIÉRON. Translated by J. B. Miner. Pp. 190. London: Kegan Paul, Trench, Trübner and Co. 1929. Price 10s. 6d.

This latest edition to the rapidly growing library of psychological textbooks is characterized by the lucid exposition of the author and his effort to apply, as far as possible, objective methods to the scientific study of mental functions. After two chapters, in which he deals with reactions and forms of behaviour, including instinctive reactions and sentiments, he discusses perceptions, the acquisition and elaboration of experience, the factors that determine mental efficiency, mental evolution and mental types. His treatment of the subject is developed on biological lines rather than on those of classical psychology, and the student consequently feels he is in closer contact with the subjects discussed than is the case in most textbooks. The translator has presented the book in readable and accurate English.

The Mott Memorial Volume. Contributions to Psychiatry, Neurology and Sociology. Pp. 401. London: H. K. Lewis. 1929. Price 21s.

The colleagues, friends and former pupils of the late Sir Frederick Mott have published in memory of him, in this handsome volume, a number of original papers, mainly on subjects in which Mott himself was particularly interested. The chief contributions to neurology are the articles by Winkler on the anatomical changes that follow removal of the cerebellum, that of Golla and Cook on an isometric study of the knee-jerk, Elliot Smith's contribution on variations in the folding of the visual cortex, and McCowan and Cook's study of the ocular symptoms of epidemic encephalitis. Most of the other contributions deal with psychiatric or sociological problems. Von Monakow has written a short history of Mott's life and a critical appreciation of the permanent value of his scientific work.

Die Blut-Liquorschranke. Eine physiologische und klinische Studie. Von P. Fr. K. WALTER. S. 223. Leipzig: Georg Thieme. 1929. Price 19 Marks.

That a monograph of this size can be written on the formation of the cerebrospinal fluid and what used to be called "meningeal permeability" is evidence of the great advances which have been made since Mestrezat published his first papers on the subject twenty years ago. To these advances the author has contributed with his bromide test, the value of which in the diagnosis of cerebral arteriosclerosis is now generally recognized. The book is not merely an apologia for this test, although the last half deals with little else, but is a fully documented account of all the work that has been done on the formation of the cerebrospinal fluid, and on what Lina Stern calls the "hæmato-encephalic barrier."

The first part of the book is devoted to the question whether the barrier between blood and cerebrospinal fluid acts as a Donnan membrane, or whether it possesses powers of selective filtration. Mestrezat was on the whole in favour of the former hypothesis, but Stern found definite evidence of selective action. Walter finds it difficult to accept the Donnan membrane theory as a complete explanation, but considers that all the factors acting on the blood side of the barrier (adsorption to proteins, rapid elimination, &c.) have not yet been fully examined. The value of his bromide permeability test depends on the answer to this question, for if bromide is treated differently from other salts it is not a satisfactory test for general plexus-meningeal permeability. He finds, however, that the results given by it are in accord with those of the older methods, and considers that the theoretical objections based on Stern's work are not sufficient to condemn the test, especially since there may be unexplained factors in her work which vitiate her results.

The bibliography given appears to be fairly complete as far as German literature is concerned but omits several of Mestrezat's early papers, and some important recent English and American references.

Le Liquide céphalo-rachidien. Par Dr. Rizer. Pp. 250 avec 24 figs
Paris: Masson et Cie. 1929. Price 28 francs.

This book embodies the results of some years of intensive study of the cerebrospinal fluid and its pathways at the medical school of Toulouse. It is divided into four sections, of which the first, which deals chiefly with technique, and the last, which describes the commoner changes in the cerebrospinal fluid, are not of very special merit, although some valuable advice and information about meningococcal meningitis is to be found in the last section. The two middle sections, which deal respectively with the physiology of the fluid and with the various methods of locating tumours or obstructions by injections of gas, lipiodol or coloured solutions, are full of new and unfamiliar material. In the physiological section are to be found not only a full criticism of the American pioneer work on the subject, but also the results of many personal experiments on animals and observations on the human subject which corroborate and amplify this work. Riser was also able to corroborate many of the results of Stern's experiments on the hæmato-encephalic barrier, but disagrees with her interpretation of their meaning, taking what seems to us the only tenable view in the light of modern knowledge, that the power of selective filtration which the choroid plexus possesses is shared by all the capillaries of the central nervous system.

The section dealing with the localization of spinal and ventricular block by injection methods is also excellent. Each method is described in detail and its usefulness and disadvantages examined thoroughly. There are probably few neurologists who will not find something new and useful in this section.

Laboratory Guide to Vertebrate Dissection for Students of Anatomy. By A. B. APPLETON. Cambridge University Press. 1929. Pp. 152. Price 6s.

In this book directions are given for the dissection of the lamprey, the dogfish, necturus, the green lizard and the dog. These animals are chosen as representing a rising scale in vertebrate evolution, and species such as the teleostean fishes, frogs and birds, which have become specialized away from the main trend of evolution have been purposely omitted. This book is intended for those who have already studied elementary biology or human anatomy, and to whom the simpler dissections are familiar. Consequently we find fairly elaborate descriptions of such structures as the eye, the internal ear and the brain, and although the author does not attempt to consider the anatomy of the central nervous system in detail, the comparison of the external appearance of the brains and skulls of the species described in this book would be a useful groundwork for neurology. The absence of illustrations was no doubt essential if the price was to be kept low, but it lessens the otherwise attractive appearance of the book.

INDEX

TO

BRAIN:

A JOURNAL OF NEUROLOGY,

FOR

VOL. LII, 1929.

INDEX OF AUTHORS.

PAGE

Adie, W. J.
Lesion of third, fourth, fifth and sixth cranial nerves 539

Adie, W. J.
Pineal syndrome 544

Antonovitch, S., and Golla, F. L.
Respiratory rhythm in its relation to the mechanism of thought 491

Barnes, Stanley, and Hurst, E. W.
Hepato-lenticular degeneration 1

Beckmann, J. W., and Kubie, L. S.
Diplopia without extra-ocular palsies.. 317

Beckmann, J. W., and Kubie, L. S.
Twenty-one cases of tumour of the hypophyseal stalk 127

Bode, O. B., and Parkes Weber, F.
Dysarthria and abnormal gait 540

Clark, W. E. Le Gros.
The optic thalamus of the insectivora.. 334

Cloake, P.
Abscess of the spinal cord 530

Cloake, P.
Pituitary tumour with goitre and acromegaly 536

Critchley, M.
Abscess of the spinal cord 530

Critchley, M.
Arteriosclerosis Parkinsonism 23

Critchley, M., and Ferguson, F. R.
An heredo-familial disease resembling disseminated sclerosis 208

De Bruyn, R. S., and Stern, Ruby O.
A case of progressive hypertrophic polyneuritis of Dejerine and Sottas, with pathological examination 84

PAGE

Denny-Brown, D.
Jacksonian epilepsy 583

Denny-Brown, D.
Progressive ataxia in a child associated with a positive blood Wassermann reaction 531

De Thurzo, Eugene.
The bi-coloured guaiac test 196

Feiling, A.
Abscess of the spinal cord 581

Feiling, A.
Compression paraplegia 587

Feiling, A.
Paralysis associated with hæmophilia.. 540

Ferguson, F. R., and Critchley, M.
An heredo-familial disease resembling disseminated sclerosis 203

Garland, H. G.
Spinal caries with compression paraplegia 536

Gillespie, R. D.
Dysarthria and abnormal gait 542

Glaser, M. A.
Tumours of the pineal, corpora quadrigemina and third ventricle .. 226

Golla, F. L., and Antonovitch, S.
Respiratory rhythm in its relation to the mechanism of thought .. 491

Greenfield, J. G.
Abscess of the spinal cord 531

Greenfield, J. G.
The pathology of measles encephalitis 171

Greenfield, J. G.
Pineal syndrome 546

Guttamacher, M., and Ironside, R.
The corpus callosum and its tumours 442

Harris, K. E.
Skin reactions in cervical sympathetic paralysis 484

Harris, Wilfred, and Newcomb, W. D.
Relapsing interstitial hypertrophic polyneuritis 108

Holmes, Gordon.
Abscess of the spinal cord 531

Holmes, Gordon.
Arterial angeioma of brain 543

Holmes, Gordon.
Dysarthria and abnormal gait 542

Holmes, Gordon.
Jacksonian epilepsy.. 585

Holmes, Gordon.
Progressive ataxia in a child 532

Hurst, E. W., and Barnes, Stanley.
Hepato-lenticular degeneration 1

PAGE

Ironside, R., and Guttamacher, M.
The corpus callosum and its tumours .. 442

Ironside, R,
Jacksonian epilepsy .. 535

Ironside, R.
Lesion of third, fourth, fifth and sixth cranial nerves .. 538

Ironside, R.
Pituitary tumour, with goitre and acromegaly .. 536

Ironside, R.
Polyneuritis cranialis .. 537

Kubie, L. S., and Beckmann, J. W.
Diplopia without extra-ocular palsies .. 317

Kubie, L. S., and Beckmann, J. W.
Twenty-one cases of tumour of the hypophyseal stalk .. 127

McAlpine, Douglas.
A form of myasthenia gravis with changes in the central nervous system .. 6

Martin, J. P.
Compression paraplegia .. 537

Martin, J. P.
Family periodic paralysis .. 543

Martin, J. P.
Paralysis associated with hæmophilia .. 540

Newcomb, W. D., and Harris, Wilfred.
Relapsing interstitial hypertrophic polyneuritis .. 108

Pritchard, E. A. B.
Variations of the knee-jerk in diseases of the central nervous system .. 359

Pritchard, E. A. B.
Electromyographic studies in paralysis agitans .. 510

Rees,
Lesion of third, fourth, fifth and sixth cranial nerves .. 539

Reynolds, F. E., and Slater, J. K.
A case of cervical glioma .. 425

Reynolds, F. E.
Pathology of glioma cerebri .. 486

Riddoch, G.
Dysarthria and abnormal gait .. 542

Seddon, H. J.
Paralysis in the left lower limb associated with hæmophilia .. 539

Slater, J. E., and Reynolds, F. E.
A case of cervical glioma .. 425

Stern, Ruby O.
The histopathology of tabes dorsalis .. 295

Stern, Ruby O., and de Bruyn, R. S.
A case of progressive hypertrophic polyneuritis of Dejerine and Sottas, with pathological examination .. 84

Susman, M. M., and Ungley, C. C,
Combined degeneration of the cord .. 271

Symonds, C. P.
Arterial angeloma of brain .. 543

PAGE

Symonds, C. P.
Compression paraplegia 587

Symonds, C. P.
Family periodic paralysis with attacks on excitement 542

Symonds, C. P.
Jacksonian epilepsy 585

Symonds, C. P.
Paralysis associated with hæmophilia 540

Ungley, C. C., and Susman, M. M.
Combined degeneration of the cord 271

Weber, F. Parkes.
Arterial angeioma of brain 543

Weber, F. Parkes, and Bode, O. B.
Dysarthria and abnormal gait 540

Worster-Drought, C. C.
Lesion of third, fourth, fifth and sixth cranial nerves 589

Yealland, L. R.
Family periodic paralysis 542

Yealland, L. R.
Lesion of third, fourth, fifth and sixth cranial nerves 583

INDEX OF SUBJECTS.

Arterial angeioma of brain. C. P. Symonds 543
Arteriosclerotic Parkinsonism. Macdonald Critchley 23
Ataxia, progressive, in a child. D. Denny-Brown 581
Combined degeneration of the cord. C. C. Ungley and M. M. Susman 271
Corpus callosum and its tumours. R. Ironside and M. Guttmacher 442
Diplopia without extra-ocular palsies. L. S. Kubie and J. W. Beckmann.. .. 317
Disseminated sclerosis, an heredo-familial disease resembling. F. R. Ferguson and M. Critchley 203
Dysarthria and abnormal gait. F. Parkes Weber and O. B. Bode.. 540
Encephalomyelitis—measles—pathology of. J. G. Greenfield 171
Glioma cerebri, the pathology of. F. E. Reynolds 486
Glioma, cervical, a study of a case of. J. K. Slater and F. E. Reynolds 425
Guaiac test, the bi-coloured. Eugene de Thurzo 196
Hæmophilia, paralysis in the left lower limb, with. H. J. Seddon 539
Heredo-familial disease resembling disseminated sclerosis. F. R. Ferguson and M. Critchley 203
Hepato-lenticular degeneration. Stanley Barnes and E. W. Hurst 1
Hypophysis. Tumours of the hypophyseal stalk. J. W. Beckmann and L. S. Kubie 127
Interstitial hypertrophic polyneuritis, a case of relapsing. W. Harris and W. D. Newcomb 108
Jacksonian epilepsy provoked by stimulus to right foot or right ear. D. Denny-Brown 583

PAGE
Knee-jerk in diseases of the central nervous system. E. A. B. Pritchard .. 359
Lesion of the third, fourth, fifth and sixth cranial nerves. L. R. Yealland .. 538
Measles encephalomyelitis, the pathology of. J. G. Greenfield 171
Myasthenia gravis with changes in the central nervous system. D. McAlpine .. 6
Ophthalmoplegia. Palsy of the third, fourth, fifth and sixth nerves. L. R. Yealland 538
Ophthalomoplegia. Polyneuritis cranialis. R. Ironside 537
Optic thalamus of the insectivora, studies on the. The anterior nuclei. W. E. Le Gros Clark 334
Paralysis agitans, electromyographic studies in. E. A. B. Pritchard 510
Paralysis, family periodic, with attacks on excitement. C. P. Symonds 542
Paralysis in the left lower limb, with hæmophilia. H. J. Seddon 539
Paraplegia, compression. H. G. Garland 536
Parkinsonism, arteriosclerotic. M. Critchley 23
Pineal syndrome. W. J. Adie 544
Pituitary tumour, with goitre and acromegaly. R. Ironside 536
Polyneuritis cranialis. R. Ironside 537
Polyneuritis, interstitial hypertrophic. W. Harris and W. D. Newcomb 108
Polyneuritis, progressive hypertrophic, with pathological examination. R. S. de Bruyn and Ruby S. Stern 84
Progressive lenticular degeneration. Stanley Barnes and E. W. Hurst 1
Respiratory rhythm in its relation to the mechanism of thought. F. L. Golla and S. Antonovitch 491
Skin reactions in cervical sympathetic paralysis. K. E. Harris 484
Spinal caries with compression paraplegia. H. G. Garland 536
Spinal cord, chronic abscess of the. M. Critchley 530
Sympathetic paralysis, cervical skin reactions in. K. E. Harris 484
Tabes dorsalis, the histopathology of. Ruby O. Stern 295
Thought, the mechanism of, and its relation to respiratory rhythm. F. L. Golla and S. Antonovitch 491
Tumour, cerebral. Tumour of the corpus callosum. R. Ironside and M. Guttmacher 442
Tumours, cerebral. Glioma cerebri. F. E. Reynolds 486
Tumours, cerebral. Pineal tumour. W. J. Adie 544
Tumours, cerebral. Tumours of the pineal, corpora quadrigemina and third ventricle. M. A. Glaser 226
Tumours of the hypophyseal stalk. J. W. Beckman and L. S. Kubie 127
Tumours of the pineal, corpora quadrigemina and third ventricle M. A. Glaser - 226
Tumours, spinal, cervical glioma. J. K. Slater and F. E. Reynolds 425
Wilson's disease, hepato-lenticular degeneration. Stanley Barnes and E. W. Hurst 1

INDEX OF NOTICES OF BOOKS.

INDEX OF AUTHORS.

PAGE

Alexander, G., Marburg, O., and Brunner, H.
Handbuch der Neurologie des Ohres 547

Anderson, J.
How to stain the nervous system 120

Appleton, A. E.
Laboratory guide to vertebrate dissection for students of anatomy 552

Bailey, P., and Cushing, Harvey.
Tumours arising from the blood-vessels of the brain. Angiomatous tumours and hæmangioblastomas 117

Berze, Josef, und Gruhle, Hans W.
Psychologie der Schizophrenie 269

Bourgeois, P.
La Myasthénie. Maladie d'Erb-Goldflam 266

Brain, W. R., and Strauss, E. B.
Recent advance in neurology 268

Brunner, H., Alexander, G., and Marburg, O.
Handbuch der Neurologie des Ohres 547

Bumke, Oswald.
Die Gegenwärtigen Strömungen in der Psychiatrie 122

Bumke, Oswald.
Handbuch der Geisteskrankheiten 120

Cairns, Hugh.
A study of intracranial surgery 125

Cobb, Stanley, and Lennox, W. C.
Epilepsy from the standpoint of physiology and treatment 118

Coghill, G. E.
Anatomy and the problem of behaviour 119

Culpin, M.
Medicine and the man 269

Cushing, Harvey, and Bailey, Percival.
Tumours arising from the blood-vessels of the brain. Angiomatous tumours and hæmangioblastomas 117

Devine, H.
Recent advance in psychiatry 268

Ebaugh, F. G., and Strecker, E. A.
Practical clinical psychiatry 123

Economo, C. von.
The cytoarchitectonics of the human cerebral cortex 117

PAGE

Economo, C. von
Die Encephalitis lethargica; ihre Nachkrankheiten und ihre Behandlung .. 549

Foerster, O.
Die Symptomatologie der Schussverletzungen der Peripheren Nerven 268
Die Therapie der Schussverletzungen der Peripheren Nerven 268

Fribourg-Blanc.
Malaria provoquée 548

Gruhle, Hans, W., und Berze, Josef.
Psychologie der Schizophrenie 269

Hamer, Sir William.
Epidemiology: Old and New 266

Jakob, Prof. Dr. A.
Spezielle Histopathologie des Grosshirns 262

Jung, C. G.
Two Essays on Analytical Psychology 122

Kroll, M.
Die neuropathologischen Syndrome 265

Lashley, K. S.
Brain mechanisms and Intelligence 548

Leibowitz, O.
Reflexmechanismus spastischer Lähmungen 266

Lennox, W. C., and Cobb, Stanley.
Epilepsy from the Standpoint of Physiology and Treatment 118

Lortat-Jacob et Poumeau-Delille.
La Syphilis médullaire 548

Marburg, O., Brunner, H. und Alexander, G.
Handbuch der Neurologie des Ohres 547

Neustadt, Rudolf.
Die Psychosen der Schwachsinnigen 123

Nobécourt, P.
Clinique médicale des enfants. Affections du système nerveux 267

Papez, J. B.
Comparative neurology 264

Piéron, H.
Principles of experimental psychology 550

Poumeau-Delille et Lortat-Jacob.
La syphilis médullaire 548

Prinzhorn, Hans.
Psychotherapie 270

Riser, Dr.
Le liquide céphalo-rachidien 551

Rosenfeld, Professor M.
Die Störungen des Bewusstseins 124

Schjelderup, H. K.
Psychologie 125

Schlesinger, B.
Die Vorder- und Mittelhirnganglien des Menschen als plastische Gebilde .. 119

PAGE

Schneider, Kurt.
Die psychopathischen Persönlichkeiten 124

Stockert, F. G.
Ueber Umbau und Abbau der Sprache bei Geistesstörung 270

Stöhr, P., Junr.
Mikroskopische Anatomie des Vegetatives Nervensystems 126

Stransky, Erwin,
Subordination, Autorität Psychotherapie 122

Strauss, E. B., and Brain, W. R.
Recent advance in neurology 268

Strecker, E. A., and Ebaugh, F. G.
Practical clinical psychiatry 123

Tredgold, A. F.
Mental deficiency 549

Walter, Fr. K.
Die Blut-Liquorschranke. Eine physiologische und klinische Studie 550

Wilson, Albert.
The Child of Circumstance 125

INDEX OF SUBJECTS.

Anatomy and the problem of behaviour. G. E. Coghill 119
Anatomy. Die Vorder- und Mittelhirnganglien des Menschen als plastische Gebilde. B. Schlesinger 119
Anatomy. Mikroskopische Anatomie des Vegetatives Nervensystems. P. Stöhr .. 126
Brain mechanism and intelligence. K. S. Lashley 548
Cerebrospinal fluid. Die Blut-Liquorschranke. Eine physiologische und klinische Studie. Fr. K. Walter 550
Cerebrospinal fluid. Le liquide céphalo-rachidien. Dr. Riser 551
Cytoarchitectonics of the human cerebral cortex, the. C. von Economo 117
Dissection, laboratory guide to vertebrate, for students of anatomy. A. E. Appleton .. 552
Encephalitis lethargica; ihre Nachkrankheiten und ihre Behandlung. C. von Economo 549
Epidemiology: Old and new. Sir William Hamer 266
Epilepsy, from the standpoint of physiology and treatment. W. G. Lennox and Stanley Cobb 118
Intercranial surgery, a study of. Hugh Cairns 125
Mental deficiency. A. F. Tredgold 549
Mott memorial volume, the. Contributions to psychiatry, neurology and sociology .. 550
Myasthénie, La. Maladie d'Erb-Goldflam. R. Bourgeois 266
Nervous system, how to stain the. J. Anderson 120
Neurology, comparative. A manual and a text-book for the nervous system of vertebrates. J. B. Papez 264
Neurology. Handbuch der Neurologie des Ohres. G. Alexander, O. Marburg und H. Brunner 547
Neurology, recent advance in. W. R. Brain and E. B. Strauss 268
Neurology. Lewandowsky's Handbuch der Neurologie. O. Foerster 263
Neurology. Die Neuropathologishen Syndrome. M. Kroll 265
Neurology. Affections du Système nerveux. Clinique médicale des enfants. P. Nobécourt 267

PAGE

Paralysis, spastic. Reflexmechanismus spastischer Lähmungen. O. Leibowitz .. 266
Pathology. Spezielle Histopathologie des Grosshirns. Professor Dr. A. Jakob .. 262
Psychiatry, recent advance in. H. Devine 268
Psychiatry. Gegenwärtigen Strömungen in der Psychiatrie. Oswald Bumke .. 122
Psychiatry. Handbuch der Geisteskrankheiten. Oswald Bumke 120
Psychiatry. Persönlichkeiten, Die psychopathischen. Kurt Schneider 124
Psychiatry, practical clinical. E. A. Strecker and F. G. Ebaugh 123
Psychiatry. Psychosen der Schwachsinnigen, Die. Rudolph Neustadt 123
Psychologie H. K. Schjelderup 125
Psychologie der Schizophrenie. Josef Berze und Hans W. Gruhle 269
Psychology, analytical, two essays on. C. G. Jung 122
Psychology. Principles of experimental psychology. H. Piéron 550
Psychology. Subordination, Autorität Psychotherapie. Erwin Stransky 122
Psychology. Medicine and the Man. M. Culpin 269
Psychology. Störungen des Bewusstseins, Die. Prof. M. Rosenfeld 124
Psychotherapie. H. Prinzhorn 270
Sociology. The Child of Circumstance. Albert Wilson 125
Speech. Ueber Umbau und Abbau der Sprache bei Geistesstörung. Dr. F. G. Stockert 270
Syphilis. La Syphilis médullaire. Lortat-Jacob et Poumeau-Delille 548
Treatment. Malaria provoquée. Fribourg-Blanc 548
Tumours arising from the blood-vessels of the brain. Angiomatous tumours and hæmangioblastomas. H. Cushing and P. Bailey 117

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-91, Great Titchfield Street, London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I to XXIII inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.